



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : <b>C07D 401/12, 401/14, 409/14, 417/14, 235/28, 471/04, A61K 31/4184, 31/4439</b>		<b>A1</b>	(11) International Publication Number: <b>WO 00/09498</b>
			(43) International Publication Date: 24 February 2000 (24.02.00)
(21) International Application Number: PCT/US99/18048 (22) International Filing Date: 9 August 1999 (09.08.99) (30) Priority Data: 09/131,481      10 August 1998 (10.08.98)      US 09/364,381      29 July 1999 (29.07.99)      US (71) Applicant: PARTNERSHIP OF MICHAEL E. GARST, GEORGE SACHS AND JAI MOO SHIN [US/US]; 2627 Raqueta, Newport Beach, CA 92660 (US). (72) Inventors: GARST, Michael, E.; 2627 Raqueta, Newport Beach, CA 92660 (US). SACHS, George; 17986 Boris Drive, Encino, CA 91316 (US). SHIN, Jai, Moo; 18833 Nau Avenue, Northridge, CA 91326 (US). (74) Agents: KLEIN, Howard, J. et al.; Klein & Szekeres, LLP, Suite 700, 4199 Campus Drive, Irvine, CA 92612 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: PRODRUGS OF PROTON PUMP INHIBITORS			
(57) Abstract			
<p>Prodrugs of the pyridyl methyl sulfinyl benzimidazole type proton pump inhibitor drugs have a hydrolyzable sulfinyl or arylsulfonyl group attached to the benzimidazole nitrogen, or include a group that forms a <i>Mannich</i> base with the benzimidazole nitrogen. The prodrugs of the invention hydrolyze under physiological conditions to provide the proton pump inhibitors with a half life measurable in hours, and are capable of providing sustained plasma concentrations of the proton pump inhibitor drugs for longer time than presently used drugs. The generation of the proton pump inhibitor drugs from the prodrugs of the invention under physiological conditions allows for more effective treatment of several diseases and conditions caused by gastric acid secretion.</p>			

***FOR THE PURPOSES OF INFORMATION ONLY***

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

## PRODRUGS OF PROTON PUMP INHIBITORS

### BACKGROUND OF THE INVENTION

#### 3. Cross-reference to Related Application

The present application is a continuation-in-part of application serial number 09/131,481, filed on August 10, 1998.

#### 2. Field of the Invention

The present invention is directed to prodrugs of proton pump inhibitors which are useful as anti-ulcer agents. More particularly, the present invention is directed to prodrugs that slowly hydrolyze to provide benzimidazole-type proton pump inhibitors which inhibit exogenously or endogenously gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases in mammals, including humans.

#### 3. Brief Description of the Prior Art

Benzimidazole derivatives intended for inhibiting gastric acid secretion are disclosed in the United States Patent Nos. 4,045,563; 4,255,431; 4,628,098; 4,686,230; 4,758,579; 4,965,269; 5,021,433; 5,430,042 and 5,708,017. Generally speaking, the benzimidazole-type inhibitors of gastric acid secretion work by undergoing a rearrangement to form a thiophilic species which then covalently binds to gastric H,K-ATPase, the enzyme involved in the final step of proton production in the parietal cells, and thereby inhibits the enzyme. Compounds which inhibit the gastric H,K-ATPase enzyme are generally known in the field as "proton pump inhibitors" (PPI).

Some of the benzimidazole compounds capable of inhibiting the gastric H,K-ATPase enzyme have found substantial use as drugs in human medicine and are known under such names as LANSOPRAZOLE (United States Patent No. 4,628,098), OMEPRAZOLE (United States Patent Nos. 4,255,431 and 5,693,818), PANTOPRAZOLE (United States Patent No. 4,758,579), and RABEPRAZOLE (United States Patent No. 5,045,552). The diseases treated

1 by proton pump inhibitors and specifically by the four above-mentioned drugs  
2 include peptic ulcer, heart burn, reflux esophagitis erosive esophagitis, non-  
3 ulcer dyspepsia, infection by *Helicobacter pylori*, alrnyitis and asthma among  
4 others.

5       Whereas the proton pump inhibitor type drugs represent substantial  
6 advance in the field of human and veterinary medicine, they are not totally  
7 without shortcomings or disadvantages. The shortcomings of the presently  
8 used proton pump inhibitor (PPI) type drugs can be best explained by a more  
9 detailed description of the mode of their action, the diseases or condition  
10 against which they are employed and the circumstances of their application.  
11 Thus, acid related diseases include but are not limited to erosive esophagitis,  
12 esophageal reflux, gastric and duodenal ulcer, non-ulcer dyspepsia and  
13 infection by *Helicobacter pylori*. Current therapy of all but the infection by *H.*  
14 *pylori* bacteria involves treatment with drugs designed to suppress acid  
15 secretion, one type of which are the above-mentioned proton pump inhibitors.

16       The presently used proton pump inhibitors are pyridyl methyl sulfinyl  
17 benzimidazoles (or compounds of closely related structure) with a  $pK_a$  of 4.0  
18 to 5.0. Their mechanism of action requires accumulation in the acidic space  
19 of the parietal cell (secretory canaliculus, pH ca. 1.0) and subsequently  
20 hydrogen ion catalyzed conversion to the reactive thiophilic species that is  
21 capable of inhibiting the gastric ATPase, enzyme resulting in effective  
22 inhibition of gastric secretion. Because of this mechanism the presently used  
23 PPI type drugs require specialized gastro protection to remain active for  
24 duodenal absorption. For this reason, and due to sensitivity to degradation in  
25 the acid milieu of the stomach, oral formulations of the PPI drugs are usually  
26 enteric coated. The need for enteric coating is a shortcoming because enteric  
27 coating is expensive and moisture sensitive.

28       Because of the requirement for accumulation in the acid space of the

1 parietal cell, acid secretion is necessary for the efficacy of the PPI type drugs.  
2 It was found that the plasma half life of these drugs is between 60 to 90  
3 minutes. All acid pumps are not active at any one time, rather only about 75  
4 % are active on the average during the time the drug is present in the blood  
5 following oral administration. It was also found in medical experience that on  
6 a currently used once-a-day oral administration therapy the maximal  
7 inhibition of stimulated acid output is approximately 66 %. This is due to a  
8 combination of the short plasma half life of the drug, to the limited number of  
9 acid pumps active during presentation of the drug and to the turn-over of acid  
10 pumps. In present practice it is not possible to control night time acid  
11 secretion by evening therapy of oral administration because the drug is  
12 dissipated from the plasma by the time acid secretion is established after  
13 midnight. The ideal target for healing in acid related diseases and for  
14 treatment of *H. pylori* infection (in conjunction with antibiotics), as well as for  
15 relief of symptoms of non-ulcer dyspepsia would be full inhibition of acid  
16 secretion. With the currently used PPI type drugs this is achieved only by  
17 intravenous infusion; in case of the drug OMEPRAZOLE this requires  
18 intravenous infusion of 8 mg per hour. Clearly, there is a need in the art for a  
19 drug or drugs acting through the mechanism of PPI -type drugs which can  
20 attain or approach full inhibition of acid secretion through oral therapy.

21 Because of the less than full inhibition of acid secretion and less than  
22 24 hour inhibition through oral administration that is attained by the current  
23 dosage forms of currently used PPI-type drugs, therapy for healing of gastric  
24 and duodenal ulcerations is 4 to 8 weeks. This is in spite of the fact that the  
25 generation time of surface cells of the esophagus, stomach and duodenum is  
26 approximately 72 hours. Undoubtedly the presently observed prolonged  
27 healing times with these drugs is due to inadequate acid suppression and acid  
28 related damage. The foregoing underscores the need in the art for a drug or

1 drugs acting through the mechanism of PPI -type drugs which can attain or  
2 approach full inhibition of acid secretion through oral therapy.

3 As further pertinent background to the present invention, applicants  
4 note the concept of prodrugs which is well known in the art. Generally  
5 speaking, prodrugs are derivatives of *per se* drugs, which after administration  
6 undergo conversion to the physiologically active species. The conversion may  
7 be spontaneous, such as hydrolysis in the physiological environment, or may  
8 be enzyme catalyzed. From among the voluminous scientific literature  
9 devoted to prodrugs in general, the foregoing examples are cited: **Design of**  
10 **Prodrugs** (Bundgaard H. ed.) 1985 Elsevier Science Publishers B. V.  
11 (Biomedical Division), Chapter 1; **Design of Prodrugs: Bioreversible**  
12 **derivatives for various functional groups and chemical entities** (Hans  
13 Bundgaard); *Bundgaard et al. Int. J. of Pharmaceutics* 22 (1984) 45 - 56  
14 (Elsevier); *Bundgaard et al. Int. J. of Pharmaceutics* 29 (1986) 19 - 28  
15 (Elsevier); *Bundgaard et al. J. Med. Chem.* 32 (1989) 2503 - 2507 **Chem.**  
16 **Abstracts 93**, 137935y (*Bundgaard et al.*); **Chem. Abstracts 95**, 138493f  
17 (*Bundgaard et al.*); **Chem. Abstracts 95**, 138592n (*Bundgaard et al.*);  
18 **Chem. Abstracts 110**, 57664p (*Alminger et al.*); **Chem. Abstracts 115**,  
19 64029s (*Buur et al.*); **Chem. Abstracts 115**, 189582y (*Hansen et al.*);  
20 **Chem. Abstracts 117**, 14347q (*Bundgaard et al.*); **Chem. Abstracts 117**,  
21 55790x (*Jensen et al.*); and **Chem. Abstracts 123**, 17593b (*Thomsen et al.*).

22 As far as the present inventors are aware, there are no prodrugs of the  
23 proton pump inhibitors presently in use. However, several United States  
24 patents describe compounds which can act as prodrugs of certain proton pump  
25 inhibitors. Specifically, United States Patent No. 4,686,230 (*Rainer et al.*)  
26 describes derivatives of pyridyl methyl sulfinyl benzimidazoles which include  
27 a group designated "R<sub>5</sub>" on one of the benzimidazole nitrogens. The "R<sub>5</sub>"  
28 group is expected to cleave under physiological condition, or under the

1 influence of an enzyme to provide the corresponding compound with a free N-  
2 H bond (see column 3 of United States Patent No. 4,686,230). United States  
3 Patent Nos. 5,021,433 (*Alminger et al.*), 4,045,563 (*Berntsson et al.*),  
4 4,965,269 and (*Brändström et al.*) also describe pyridyl methyl sulfinyl  
5 benzimidazoles where one of the nitrogens of the benzimidazole moiety bears  
6 a substituent that cleaves under physiological or enzymatic conditions.

7 The present invention represents further advance in the art in that it  
8 provides prodrugs of improved structure of the proton pump inhibitor type  
9 drugs and provides proof of the suitability of the prodrugs of the invention for  
10 use as prodrug of proton pump inhibitors, with improved efficacy in therapy of  
11 acid related diseases due to prolongation of the presence of the proton pump  
12 inhibitors in the body.

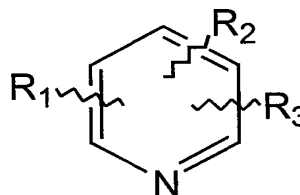
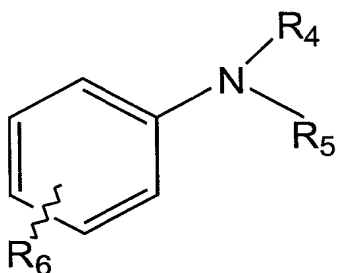
### 13 SUMMARY OF THE INVENTION

14 The present invention relates to compounds of **Formula 1**

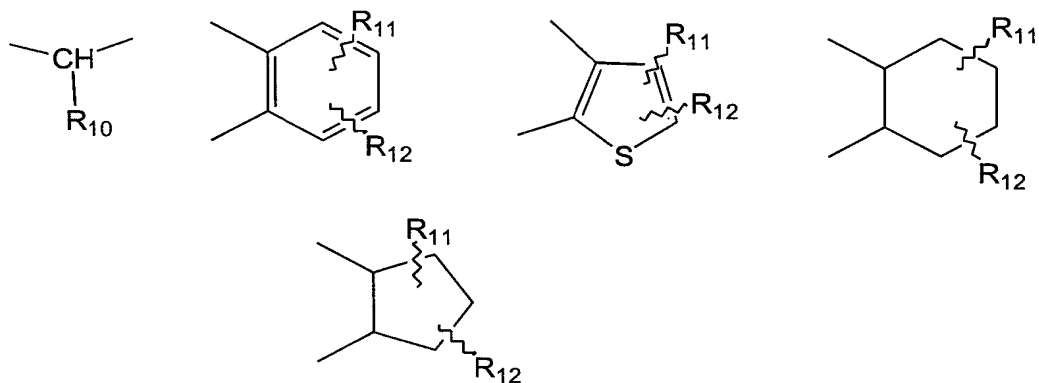


16 wherein

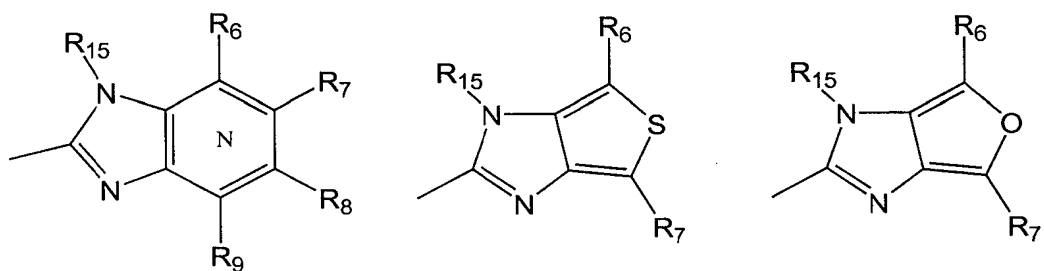
17  $\text{Het}_1$  is selected from the formulas shown below



X is selected from the formulas



and  $\text{Het}_2$  is selected from the formulas





1           where N in the benzimidazole moiety means that one of the ring  
2   carbons may be exchanged for an unsubstituted N atom;

3            $R_1$ ,  $R_2$  and  $R_3$  are independently selected from hydrogen, alkyl of 1  
4   to 10 carbons, fluoro substituted alkyl of 1 to 10 carbons, alkoxy of 1 to 10  
5   carbons, fluoro substituted alkoxy of 1 to 10 carbons, alkylthio of 1 to 10  
6   carbons, fluoro substituted alkylthio of 1 to 10 carbons, alkoxyalkoxy of 2 to  
7   10 carbons, amino, alkylamino and dialkylamino each of the alkyl groups in  
8   said alkylamino and dialkyl amino groups having 1 to 10 carbons, halogen,  
9   phenyl, alkyl substituted phenyl, alkoxy substituted phenyl, phenylalkoxy,  
10   each of the alkyl groups in said alkyl substituted phenyl, alkoxy substituted  
11   phenyl and phenylalkoxy having 1 to 10 carbons, piperidino, morpholino or  
12   two of the  $R_1$ ,  $R_2$  and  $R_3$  groups jointly forming a 5 or 6 membered ring  
13   having 0 or 1 heteroatom selected from N, S and O;

14            $R_4$  and  $R_5$  are independently selected from hydrogen, alkyl of 1 to 10  
15   carbons, fluoro substituted alkyl of 1 to 10 carbons, phenylalkyl, naphthylalkyl  
16   and heteroarylalkyl, alkyl in said phenylalkyl, naphthylalkyl and  
17   heteroarylalkyl groups having 1 to 10 carbons;

18            $R_6$  is hydrogen, halogen, alkyl of 1 to 10 carbons, fluoro substituted  
19   alkyl of 1 to 10 carbons, alkoxy having 1 to 10 carbons or fluoro substituted  
20   alkoxy having 1 to 10 carbons;

21            $R_6$  through  $R_9$  are independently selected from hydrogen, halogen,  
22   alkyl of 1 to 10 carbons, halogen substituted alkyl of 1 to 10 carbons, alkoxy  
23   of 1 to 10 carbons, halogen substituted alkoxy of 1 to 10 carbons,  
24   alkylcarbonyl, alkoxycarbonyl the alkyl group in said alkylcarbonyl and  
25   alkoxycarbonyl having 1 to 10 carbons, oxazolyl, imidazolyl, thiazolyl,  
26   morpholinyl, piperazinyl, pyrazinyl, pyrazolyl, or any two adjacent ones of the  
27    $R_6$  through  $R_9$  groups may form a ring that may optionally include a

1 heteroatom selected from N, O and S and said ring may be further substituted;

2  $R_{10}$  is hydrogen, alkyl of 1 to 10 carbons, or  $R_{10}$  may form an alkylene  
3 chain together with  $R_3$ ,

4  $R_{11}$  and  $R_{12}$  are independently selected from hydrogen, halogen, alkyl  
5 of 1 to 10 carbons and halogen substituted alkyl of 1 to 10 carbons;

6  $R_{15}$  is selected from the formulas below

7

8

9

10

11

12

13

14

15

16

17 where

18  $R_{16}$  is alkyl of 1 to 10 carbons, morpholino, piperidino, phenyl,

19 naphthyl or heteroaryl having 1 to 3 heteroatoms selected from N, O or S, said

20 morpholino, piperidino phenyl, naphthyl or heteroaryl groups being

21 unsubstituted, or substituted with 1 to 5  $R_{17}$  groups;

22  $R_{17}$  is alkyl of 1 to 10 carbons, halogen substituted alkyl of 1 to 10

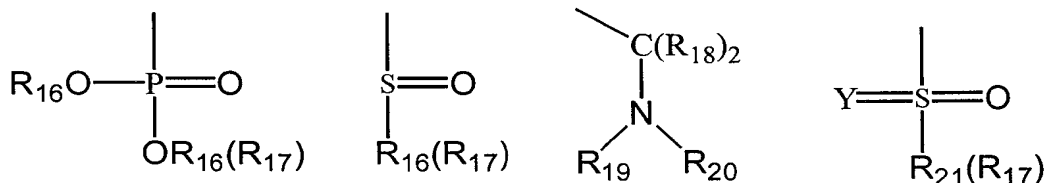
23 carbons, alkoxy having 1 to 10 carbons, halogen substituted alkoxy of 1 to 10

24 carbons, alkylthio having 1 to 10 carbons, halogen substituted alkylthio of 1 to

25 10 carbons, alkoxy carbonyl having 1 to 10 carbons, halogen substituted

26 alkoxy carbonyl having 1 to 10 carbons, F, Cl, Br, I,  $NO_2$ , CN, OCOalkyl,

27  $NH_2$ , alkylamino and dialkylamino where in said OCOalkyl, , alkylamino and



1   dialkylamino groups each of said alkyl group has 1 to 10 carbons, further  $R_{17}$   
2   is ureidoyl (RNHCONH-), guanidiny, carbamoyl, N-substituted carbamoyl,  
3   alkylcarbonyl having 1 to 10 carbons, (alkoxycarbonyl)alkoxy groups of each  
4   of said alkoxy group has 1 to 10 carbons, (alkoxycarbonyl)alkyl groups of  
5   each of said alkoxy or alkyl group has 1 to 10 carbons, (carbamoyl)alkoxy  
6   having 1 to 10 carbons, (N-alkylcarbamoyl)alkoxy having 1 to 10 carbons,  
7   (N,N-dialkylcarbamoyl)alkoxy having 1 to 10 carbons, (N-substituted or  
8   unsubstituted carbamoyl)poly(alkoxy) having 1 to 10 carbons, (N-substituted  
9   or unsubstituted carbamoyl)alkyl having 1 to 10 carbons, [N-  
10   (heteroaryl)carbamoyl]alkyl having 1 to 10 carbons, [N-  
11   (heteroaryl)carbamoyl]alkoxy having 1 to 10 carbons, [N-(substituted  
12   heteroaryl)carbamoyl]alkoxy having 1 to 10 carbons, [N-(substituted  
13   aryl)carbamoyl]alkoxy having 1 to 10 carbons, poly(alkoxy) group of each of  
14   said alkoxy group has 1 to 10 carbons, cyclic polyalkoxy (such as crown ether  
15   moiety), guanidiny group, ureido group, dialkylamino-poly(alkoxy) group,  
16   [N-(carbamoylalkyl)carbamoyl]alkoxy, [N-(carbamoylalkyl)carbamoyl]alkyl,  
17   [N-[[N-(heteroaryl) carbamoyl]alkyl]carbamoyl]alkoxy, [N-[[N-(substituted  
18   heteroaryl) carbamoyl]alkyl]carbamoyl]alkoxy, [(tri-alkyl)ammonium]-  
19   alkoxy, (sulfonato)alkyl, (sulfonato)alkoxy, N-[sulfonato)alkyl]amido,  
20   (substituted)maleimido-, (substituted)succinimido;  
21        $R_{18}$  is independently selected from H, alkyl of 1 to 10 carbons and  
22   phenyl;  
23        $R_{19}$  and  $R_{20}$  are independently selected from H, alkyl of 1 to 10  
24   carbons, halogen substituted alkyl of 1 to 10 carbons, or  $R_{19}$  and  $R_{20}$  together  
25   with the N atom may form a 4 to 10 membered ring that may include one more  
26   heteroatom selected from N, O or S, said N heteroatom being unsubstituted or  
27   substituted with an alkyl group of 1 to 10 carbons, or with an aryl or heteroaryl  
28   group, and

1            $R_{21}$  is alkyl, (aryl)alkyl, (heteroaryl)alkyl, phenyl, naphthyl or  
2 heteroaryl having 1 to 3 heteroatoms independently selected from N, O and S,  
3 said phenyl, naphthyl or heteroaryl groups being unsubstituted or substituted  
4 with 1 to 5  $R_{17}$  groups,  
5           Y is O or  $=NR_{16}$ ,  
6           or to a pharmaceutically acceptable salt of said compounds.  
7           The compounds of the invention are sulfoxides and have an asymmetric  
8 center in the sulfur atom. Both the pure enantiomers, racemic mixtures and  
9 unequal mixtures of the two are within the scope of the present invention.  
10          Some of the compounds of the invention may have one or more asymmetric  
11 carbon atoms (for example in a branch-chained alkyl group) and some other  
12 compounds may have a second sulfoxide providing still another asymmetric  
13 center in the sulfur atom. All optical isomers, racemates, diastereomers and  
14 their mixtures are within the scope of the invention.  
15          The compounds of the invention act as prodrugs of proton pump  
16 inhibitor type drugs which are useful for inhibiting gastric acid secretion. The  
17 compounds of the invention have excellent stability in tablet or capsule form,  
18 are acid stable, have excellent bioavailability and plasma half life extending up  
19 to 5 - 6 hours which is significantly longer than the plasma half life of the  
20 presently used proton pump inhibitors.

## 21           DETAILED DESCRIPTION OF THE INVENTION

22          The chemical structure of the compounds of the invention is shown and  
23 described in broad terms in the Summary of the Invention in connection with  
24 **Formula 1**. As it can be seen in the formula, the compounds of the invention  
25 are pyridyl methyl sulfinyl benzimidazoles, or compounds of closely related  
26 structure, wherein one of the benzimidazole nitrogens is substituted with a  
27 group (designated  $R_{15}$  in **Formula 1**) that gradually cleaves under  
28 physiological conditions and thereby provides the pyridyl methyl sulfinyl

1 benzimidazole compound (or compound of closely related structure) which  
2 has a free N-H function in the benzimidazole (or related) moiety. The  
3 compound thus obtained by cleavage of the  $R_{15}$  group then undergoes the acid  
4 catalyzed rearrangement and provides the thiophilic species which inhibits the  
5 H,K-ATPase enzyme involved in gastric acid production. Thus, the novel  
6 compounds of the present invention bearing the  $R_{15}$  group are prodrugs of the  
7 proton pump inhibitor compounds which could also be depicted by **Formula**  
8 **1**, where, however the  $R_{15}$  group would be designated hydrogen.

9 Generally speaking, among the prodrugs compounds of the present  
10 invention those are preferred wherein the structure of the pyridyl methyl  
11 sulfinyl benzimidazole or structurally related moiety is also preferred in the  
12 prior art. In other words, preferably prodrugs are provided in accordance with  
13 the present invention for those proton pump inhibitor drugs which are  
14 themselves preferred.

15 Referring now to the specific designation of symbols in connection with  
16 **Formula 1**, compounds are preferred in accordance with the present invention  
17 wherein the moiety designated **Het<sub>1</sub>** is pyridyl substituted with alkyl, O-alkyl  
18 and/or O-fluoroalkyl groups. Most preferred substituents for the pyridine  
19 moiety, designated  $R_1$ ,  $R_2$  and  $R_3$  in **Formula 1**, are  $CH_3O-$ ,  $CH_3-$ ,  $CF_3CH_2O-$   
20 and  $CH_3O(CH_2)_3O-$ .

21 The moiety designated **X** in **Formula 1** is preferably a methylene (-  
22  $CH_2$  -) group, or a  $-CHR_{10}$  group and the methylene or  $-CHR_{10}$  group is  
23 preferably attached in  $\alpha$  position to the nitrogen in the pyridine moiety.  
24 Compounds where the **X** is *ortho* phenylene or substituted *ortho* phenylene  
25 are also preferred; in the most preferred compounds **X** is methylene.

26 Referring now to the group designated **Het<sub>2</sub>** in **Formula 1**, this moiety  
27 is preferably a substituted benzimidazole. The  $R_6$  through  $R_9$  groups  
28 preferably are selected from hydrogen, chlorine and fluoro-substituted alkoxy

1 groups, with hydrogen, chlorine,  $\text{CF}_2\text{HO-}$  and  $\text{CH}_3\text{O-}$  being even more  
2 preferred.

3 Referring now to the group designated  $\text{R}_{15}$  in connection with  
4 **Formula 1** it will be apparent to those skilled in the art that this group  
5 represents the principal novel structural feature of the present invention.  
6 Among the  $\text{R}_{15}$  groups shown in connection with **Formula 1** the arylsulfonyl  
7 groups (designated  $\text{R}_{21}(\text{R}_{17})\text{SOY-}$  where Y is O ) are preferred. In the  
8 arylsulfonyl groups the aryl portion ( $\text{R}_{21}$ ) is preferably phenyl, substituted or  
9 unsubstituted with the  $\text{R}_{17}$  group. When the phenyl group ( $\text{R}_{21}$ ) is substituted,  
10 then the substituent ( $\text{R}_{17}$ ) is preferably selected from Cl, Br, F, lower alkyl,  
11 lower alkoxy, trifluoromethyl, trifluoromethoxy, di-(lower alkyl)amino, lower  
12 alkoxycarbonyl, ureidoyl ( $\text{RNHCONH-}$ ), guanidiny, carbamoyl, N-substituted  
13 carbamoyl, (N-substituted carbamoyl)alkyl, di-(lower alkylamino)alkoxy,  
14 (morpholin-4-yl)alkoxy, (morpholin-4-yl)polyalkoxy, di-(lower  
15 alkylamino)alkyl, poly(alkoxy)alkoxy, cyclic poly(alkoxy),  
16 (carbamoyl)alkoxy, [(N-(lower alkyl)carbamoyl]alkoxy, [N,N-(lower  
17 dialkyl)carbamoyl]alkoxy, (N,N-dialkylcarbamoyl)alkyl, [N-  
18 (heteroaryl)carbamoyl]alkyl, [N-(heteroaryl)carbamoyl]alkoxy, [N-  
19 (aryl)carbamoyl]alkoxy, [N-[(N-substituted  
20 carbamoyl)alkyl]carbamoyl]alkoxy, (sulfonato)alkyl, (sulfonato)alkoxy, N-  
21 [sulfonato)alkyl]amido, (substituted)maleimido-, (substituted)succinimido and  
22 [(tri-alkyl)ammonium]-alkoxy. Even more preferably the phenyl group is  
23 unsubstituted ( $\text{R}_{17}$  is H) or the substituent of the phenyl ( $\text{R}_{21}$ ) group is selected  
24 from Cl, Br, F, methyl, methoxy, trifluoromethyl, trifluoromethoxy,  
25 dimethylamino, ethoxycarbonyl, carbamoyl, guanidiny, ureidoyl,  
26 (carbamoyl)methoxy, [N-(pyridyl)carbamoyl]methoxy, morpholinyl,  
27 (morpholin-4-yl)alkoxy, [(morpholin-4-yl)alkoxy]alkoxy, 2-  
28 (dimethylamino)ethoxy, [N-[(carbamoyl) methyl]carbamoyl]methoxy,

1 sodium(sulfonato)alkoxy, (trimethylammonium)alkoxy, poly(alkoxy), and  
2 cyclic tetra- or penta-ethyleneoxy groups. Preferably there is only one  $R_{17}$   
3 substituent (other than hydrogen) in the phenyl ( $R_{21}$ ) moiety, and preferably  
4 the  $R_{17}$  substituent is in a position *para* (1,4) or *meta* (1,3) to the sulfonyl  
5 ( $SO_2$ ) group.

6 In other embodiments of the compounds of the invention the  
7 physiologically labile substituent  $R_{15}$  is a sulfinyl group, designated  
8  $R_{16}(R_{17})SO-$  in connection with **Formula 1**. Preferred groups for the  $R_{16}(R_{17})$   
9 combination are the same as for the  $R_{21}(R_{17})$  combination, still more preferred  
10 are phenyl, 4-methylphenyl, 4-methoxyphenyl and 4-trifluoromethylphenyl.  
11 In this specification lower alkyl or lower alkoxy has 1 to 6 carbons.

12 In still other embodiments of the compounds of the invention the  
13 physiologically labile substituent  $R_{15}$  forms a *Mannich* base, designated  
14  $R_{19}R_{20}N-C(R_{18})_2-$  in connection with **Formula 1**. In these *Mannich* base type  
15 compounds  $R_{18}$  is preferably H or lower alkyl, most preferably H or methyl.  
16 The  $R_{19}R_{20}N$  groups preferably are di-(lower alkyl)amino, *N*-succinimidyl, *N*-  
17 morpholinyl, *N*-piperidinyl, *N*-(*N*-4-methyl)hexahydropyrazinyl, *N,N*-  
18 phenyl,methyl-amino, *N*-tetrahydropyrrolyl, and *N*-(benzotriazol-1-yl), as  
19 depicted below and designated respectively by formulas 2 through 8 and 8a:

20

21

22

23

24

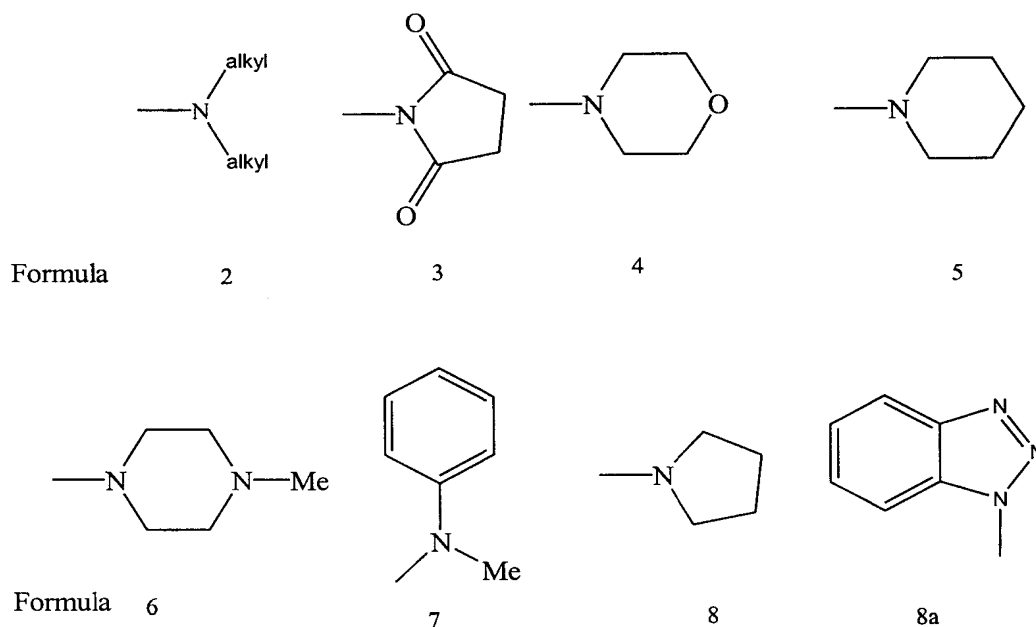
25

26

27

28

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12

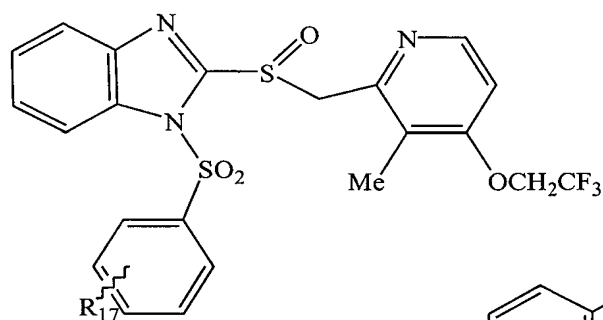
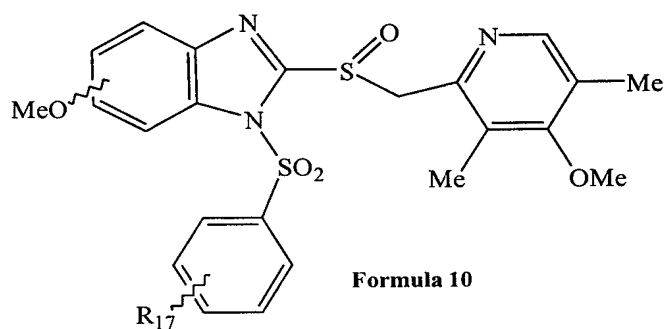


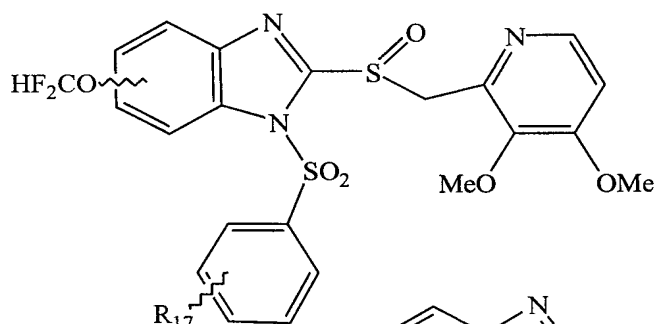
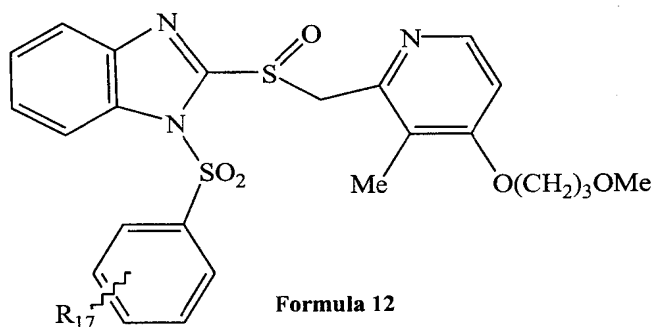
The most preferred groups for the  $R_{19}R_{20}N$ - combination in accordance with the present invention are dimethylamino, *N*-morpholino, and *N*-piperidinyl.

The most preferred compounds of the invention are those wherein the proton pump inhibitor portion is the same as in the widely used proton pump inhibitor drugs known under the names LANSOPRAZOLE, OMEPRAZOLE, PANTOPRAZOLE and RABEPRAZOLE and wherein the  $R_{15}$  group is a benzenesulfonyl group mono-substituted either in the 4 (*para*) or in the 3 (*meta*) position with a Cl, Br, F, CH<sub>3</sub>, CH<sub>3</sub>O, CF<sub>3</sub>, CF<sub>3</sub>O-, (CH<sub>3</sub>)<sub>2</sub>N NH<sub>2</sub>CO, NH<sub>2</sub>CONH, NH<sub>2</sub>C(=NH)NH, 4-morpholino, 2-(4-morpholinyl)ethoxy, 2-[2-(4-morpholinyl)ethoxy]ethoxy, 3-(4-morpholinyl)propoxy, poly(alkoxy), Na<sup>+</sup> O<sub>3</sub>S-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-O, X<sup>-</sup> (CH<sub>3</sub>)<sub>3</sub>N<sup>+</sup>CH<sub>2</sub>CH<sub>2</sub>O- (X is an anion, such as a halogen ion), NH<sub>2</sub>COCH<sub>2</sub>O, (pyridyl)NHCOCH<sub>2</sub>O, NH<sub>2</sub>COCH<sub>2</sub>NH<sub>2</sub>COCH<sub>2</sub>O, (CH<sub>3</sub>)<sub>2</sub>NCH<sub>2</sub> or EtOCO group. These compounds are shown by **Formulas 9, 10, 11 and 12**, respectively, where  $R_{17}^*$  represents said Cl, Br, F, CH<sub>3</sub>, CH<sub>3</sub>O, CF<sub>3</sub>, CF<sub>3</sub>O-, (CH<sub>3</sub>)<sub>2</sub>N, NH<sub>2</sub>CO, NH<sub>2</sub>CONH, NH<sub>2</sub>C(=NH)NH, 4-morpholino, 2-(4-morpholinyl)ethoxy, 2-[2-



1 (4-morpholinyl)ethoxy]ethoxy, 3-(4-morpholinyl)propoxy, poly(alkoxy),  
2  $\text{NH}_2\text{COCH}_2\text{O}$ , (pyridyl) $\text{NHCOCH}_2\text{O}$ ,  $\text{NH}_2\text{COCH}_2\text{NH}_2\text{COCH}_2\text{O}$ ,  $(\text{CH}_3)_2\text{NCH}_2$ ,  
3  $\text{Na}^+ \text{ } ^-\text{O}_3\text{S-CH}_2\text{CH}_2\text{CH}_2\text{-O}$ ,  $(\text{CH}_3)_3\text{N}^+\text{CH}_2\text{CH}_2\text{O-}$ , or  $\text{EtOCO}$  groups in the 4  
4 (*para*) or in the 3 (*meta*) position of the phenyl ring, and where the numbering  
5 of the benzimidazole ring is shown in the formulas. In **Formula 10** the  
6  $\text{CH}_3\text{O-}$  group can occupy the 5 or the 6 position of the benzimidazole moiety,  
7 and in **Formula 11** the  $\text{CF}_2\text{HO-}$  group can occupy the 5 or the 6 position of the  
8 benzimidazole moiety.

**Formula 9****Formula 10**

**Formula 11**

### Formula 12

The compounds of the invention include

2-[[[(3-chloro-4-morpholino-2-pyridyl)methyl]sulfinyl]-5-methoxy-(1H)-benzimidazole,

2-[[[4-(2,2,3,3,4,4,4-heptafluorobutyl)oxy]-2-pyridyl)methyl]sulfinyl]-1H-thieno[3,4-d]imidazole,

2-[[[4-ethythio-3-methyl-2-pyridyl)methyl]sulfinyl]-1h-benzimidazole

2-[(3-methoxyphenyl)methylsulfinyl]-1H-benzimidazole,

2-[(3-methoxyphenyl)methylsulfinyl]imidazo[5,4-c]pyridine,

2-[(3-methoxyphenyl)methylsulfinyl]imidazo[4,5-c]pyridine,

and 2-[(3-methoxyphenyl)methylsulfinyl]-5-nitro-benzimidazole, of which 1-position have R<sub>15</sub> group. R<sub>15</sub> group of these compounds is a benzenesulfonyl group mono-substituted either in the 4 (para) or in the 2 (meta) position with a

Cl, Br, F, CH<sub>3</sub>, CH<sub>3</sub>O, CF<sub>3</sub>, CF<sub>3</sub>O, (CH<sub>3</sub>)<sub>2</sub>N, NH<sub>2</sub>CO, NH<sub>2</sub>CONH,

NH<sub>2</sub>C(=NH)NH, 4-morpholino, 2-(4-morpholinyl)ethoxy, 2-[2-(4-

- 1 morpholinyl)ethoxy]ethoxy, 3-(4-morpholinyl)propoxy,  $\text{NH}_2\text{COCH}_2\text{O}$ ,  
2 (pyridyl) $\text{NHCOCH}_2\text{O}$ ,  $\text{NH}_2\text{COCH}_2\text{NH}_2\text{COCH}_2\text{O}$ ,  $(\text{CH}_3)_2\text{NCH}_2$ ,  
3  $\text{Na}^+ \text{O}_3\text{S-CH}_2\text{CH}_2\text{CH}_2\text{-O}$ ,  $(\text{CH}_3)_3\text{N}^+\text{CH}_2\text{CH}_2\text{O-}$ , or EtOCO group.  
4 Examples of the presently most preferred compounds of the invention are as  
5 follows:  
6 1-benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
7 pyridyl)methylsulfinyl]-1H-benzimidazole,  
8 1-benzenesulfonyl-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
9 pyridyl)methylsulfinyl]-1H-benzimidazole,  
10 1-benzenesulfonyl-5-difluoromethoxy-2-[(3,4-dimethoxy-2-  
11 pyridyl)methylsulfinyl]-1H-benzimidazole,  
12 1-benzenesulfonyl-6-difluoromethoxy-2-[(3,4-dimethoxy-2-  
13 pyridyl)methylsulfinyl]-1H-benzimidazole,  
14 1-benzenesulfonyl-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-  
15 pyridyl)methylsulfinyl]-1H-benzimidazole,  
16 1-(p-chlorobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
17 pyridyl)methylsulfinyl]-1H-benzimidazole,  
18 1-(p-chlorobenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
19 pyridyl)methylsulfinyl]-1H-benzimidazole,  
20 1-(p-chlorobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-  
21 pyridyl)methylsulfinyl]-1H-benzimidazole,  
22 1-(p-chlorobenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-  
23 pyridyl)methylsulfinyl]-1H-benzimidazole,  
24 1-(p-chlorobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-  
25 pyridyl)methylsulfinyl]-1H-benzimidazole,  
26 1-(p-bromobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
27 pyridyl)methylsulfinyl]-1H-benzimidazole,  
28 1-(p-bromobenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-

- 1 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 2 1-(p-bromobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 3 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 4 1-(p-bromobenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 5 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 6 1-(p-bromobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 7 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 8 1-(p-fluorobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 9 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 10 1-(p-fluorobenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 11 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 12 1-(p-fluorobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 13 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 14 1-(p-fluorobenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 15 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 16 1-(p-fluorobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 17 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 18 1-(p-methylbenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 19 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 20 1-(p-methylbenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 21 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 22 1-(p-methylbenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 23 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 24 1-(p-methylbenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 25 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 26 1-(p-methylbenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 27 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 28 1-(p-methoxybenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-

- 1 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 2 1-(p-methoxybenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 3 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 4 1-(p-methoxybenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 5 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 6 1-(p-methoxybenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 7 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 8 1-(p-methoxybenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 9 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 10 1-(3-trifluoromethylbenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-
- 11 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 12 1-(3-trifluoromethylbenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-
- 13 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 14 1-(3-trifluoromethylbenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-
- 15 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 16 1-(3-trifluoromethylbenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-
- 17 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 18 1-(3-trifluoromethylbenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-
- 19 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 20 1-(p-trifluoromethoxybenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-
- 21 methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 22 1-(p-trifluoromethoxybenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-
- 23 methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 24 1-(p-trifluoromethoxybenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-
- 25 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 26 1-(p-trifluoromethoxybenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-
- 27 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 28 1-(p-trifluoromethoxybenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-

- 1 trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 2 1-(p-dimethylaminobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-
- 3 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 4 1-(p-dimethylaminobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-
- 5 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 6 1-(p-dimethylaminobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-
- 7 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 8 1-(p-ethoxycarbonylbenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-
- 9 methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 10 1-(p-ethoxycarbonylbenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-
- 11 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 12 1-(pyridine-3-sulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 13 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 14 1-(pyridine-3-sulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 15 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 16 1-(pyridine-3-sulfonyl)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
- 17 pyridyl]methyl]sulfinyl]-1H-benzimidazole,
- 18 1-(pyridine-3-sulfonyl)-5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-
- 19 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 20 1-(pyridine-3-sulfonyl)-6-(difluoromethoxy)-2-[(3,4-dimethoxy-2-
- 21 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 22 1-[4-[(morpholin-4-yl)phenyl]sulfonyl]-5-methoxy-2-[(3,5-dimethyl-4-
- 23 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 24 1-[4-[(morpholin-4-yl)phenyl]sulfonyl]-6-methoxy-2-[(3,5-dimethyl-4-
- 25 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 26 N-[4-[[5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 27 pyridyl)methyl]sulfinyl]benzimidazol-1-yl]sulfonyl]phenyl]urea,
- 28 N-[4-[[6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-

- 1 pyridyl)methyl]sulfinyl]benzimidazol-1-yl]sulfonyl]phenyl]urea,  
2 N-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-  
3 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl} phenyl)urea,  
4 N-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-2-  
5 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl} phenyl)urea,  
6 N-(4-{[2-({[(3,4-di(methoxy)-2-pyridyl)methyl]sulfinyl}-5-(difluoromethoxy)-  
7 benzimidazol-1-yl]sulfonyl} phenyl)urea,  
8 N-(4-{[2-({[(3,4-di(methoxy)-2-pyridyl)methyl]sulfinyl}-6-(difluoromethoxy)-  
9 benzimidazol-1-yl]sulfonyl} phenyl)urea,  
10 15-{[2-({[4-(3-methoxypropoxy-3-methyl-2-  
11 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl}-  
12 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene,  
13 15-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-  
14 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl}-  
15 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene,  
16 15-[(5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-  
17 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]-  
18 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene,  
19 15-[(6-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-  
20 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]-  
21 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene,  
22 15-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-  
23 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]-  
24 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene,  
25 15-[(6-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-  
26 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]-  
27 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene,  
28 2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-

1 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,  
2 2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-  
3 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-  
4 pyridyl)acetamide,  
5 N-(carbamoylmethyl)-2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-  
6 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,  
7 2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-  
8 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,  
9 2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-  
10 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-  
11 pyridyl)acetamide,  
12 N-(carbamoylmethyl)-2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-  
13 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,  
14 2-(4-{2-([3-methyl-4-(2,2,2-trifluoroethoxy)-2-  
15 pyridyl]methyl} sulfinyl)benzimidazol-1-yl)sulfonyl} phenoxy)acetamide,  
16 2-(4-{2-([3-methyl-4-(2,2,2-trifluoroethoxy)-2-  
17 pyridyl]methyl} sulfinyl)benzimidazol-1-yl)sulfonyl} phenoxy)-N-(2-  
18 pyridyl)acetamide,  
19 N-(carbamoylmethyl)-2-(4-{2-([3-methyl-4-(2,2,2-trifluoroethoxy)-2-  
20 pyridyl]methyl} sulfinyl)benzimidazol-1-yl)sulfonyl} phenoxy)acetamide,  
21 2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-  
22 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,  
23 2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-  
24 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-  
25 pyridyl)acetamide,  
26 N-(carbamoylmethyl)-2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-  
27 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,  
28 2-{4-[(6-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-



1 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,  
2 2-{4-[(6-(difluoromethoxy)-2-[(3,4-dimethoxy-2-  
3 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-  
4 pyridyl)acetamide,  
5 N-(carbamoylmethyl)-2-{4-[(6-(difluoromethoxy)-2-[(3,4-dimethoxy-2-  
6 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,  
7 2-(4-{[2-([4-(3-methoxypropoxy)-3-methyl-2-  
8 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl} phenoxy)acetamide,  
9 2-(4-{[2-([4-(3-methoxypropoxy)-3-methyl-2-  
10 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl} phenoxy)-N-(2-  
11 pyridyl)acetamide,  
12 N-(carbamoylmethyl)-2-(4-{[2-([4-(3-methoxypropoxy)-3-methyl-2-  
13 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl} phenoxy)acetamide,  
14 1-[[ 4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-5-(difluoromethoxy)-2-  
15 [[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,  
16 1-[[ 4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-6-(difluoromethoxy)-2-  
17 [[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,  
18 1-[[ 4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-5-methoxy-2-[(3,5-  
19 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,  
20 1-[[ 4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-6-methoxy-2-[(3,5-  
21 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,  
22 1-[[ 4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-2-[(3-methyl-4-  
23 methoxypropoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,  
24 1-[[ 4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-2-[(3-methyl-4-(2,2,2-  
25 trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,  
26 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-2-[[[(4-(3-methoxypropoxy)-  
27 3-methyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,  
28 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-5-(difluoromethoxy)-2-[(3,4-

- 1 dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 2 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-5-methoxy-2-[[[(3,5-dimethyl-
- 3 4-methoxy-2-pyridyl)methyl]sulfinyl]]-1H-benzimidazole,
- 4 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-6-(difluoromethoxy)-2-[[[(3,4-
- 5 dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 6 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-6-methoxy-2-[[[(3,5-dimethyl-
- 7 4-methoxy-2-pyridyl)methyl]sulfinyl]]-1H-benzimidazole,
- 8 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-2-[[[3-methyl-4-(2,2,2-
- 9 trifluoroethoxy)-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 10 1-[{(N,N-dimethylamino)methyl}benzene-4-sulfonyl]-5-methoxy-2-[[[(3,5-
- 11 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 12 1-[2-acetamido-4-methyl-5-thiazolylsulfonyl]-5-methoxy-2-[[[(3,5-dimethyl-4-
- 13 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 14 1-(thiophene-2-sulfonyl)-5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 15 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 16 1-[{(N,N-dimethylamino)methyl}benzene-4-sulfonyl]-6-methoxy-2-[[[(3,5-
- 17 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 18 1-[2-acetamido-4-methyl-5-thiazolylsulfonyl]-6-methoxy-2-[[[(3,5-dimethyl-4-
- 19 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 20 1-(thiophene-2-sulfonyl)-6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 21 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 22 1-(thiophene-2-sulfonyl)-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-
- 23 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 24 1-(thiophene-2-sulfonyl)-5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-
- 25 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 26 1-(thiophene-2-sulfonyl)-6-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-
- 27 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 28 1-(thiophene-2-sulfonyl)-]-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-

- 1 pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 2 1-(phenylmethylsulfonyl)-5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 3 pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 4 1-(n-propanesulfonyl)-5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 5 pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 6 1-(n-butanesulfonyl)-5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 7 pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 8 1-(isopropylsulfonyl)-5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 9 pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 10 1-[(N,N-dimethylamino)benzene-4-sulfonyl]-5-methoxy-2-[[[(3,5-dimethyl-4-
- 11 methoxy-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 12 1-(phenylmethylsulfonyl)-6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 13 pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 14 1-(n-propanesulfonyl)-6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 15 pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 16 1-(n-butanesulfonyl)-6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 17 pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 18 1-(isopropylsulfonyl)-6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 19 pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 20 1-[(N,N-dimethylamino)benzene-4-sulfonyl]-6-methoxy-2-[[[(3,5-dimethyl-4-
- 21 methoxy-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 22 1-(pyridine-3-sulfonyl)-2-[[[(3-methyl-4-methoxypropoxy-2-
- 23 pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 24 1-[4-(morpholin-4-yl)phenylsulfonyl]-2-[[[(4-(3-methoxypropoxy)-3-methyl-
- 25 2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 26 1-benzenesulfonyl-2-[[[(3-chloro-4-morpholino-2-pyridyl)methyl)sulfinyl]-5-
- 27 methoxy-(1H)-benzimidazole,
- 28 1-benzenesulfonyl-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-

1 pyridyl)methyl]sulfinyl]-1H-benzimidazole,  
2 1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]-1H-benzimidazole,  
3 1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]imidazolo[5,4-  
4 c]pyridine,  
5 1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]imidazolo[4,5-  
6 c]pyridine,  
7 1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]-5-nitro-  
8 benzimidazole,  
9 1-benzenesulfonyl-2-[{2-(dimethylamino)phenyl}methylsulfinyl]-1H-  
10 benzimidazole,  
11 1-benznesulfonyl-2-[[[4-(2,2,3,3,4,4,4-heptafluorobutyl)oxy]-2-  
12 pyridyl)methyl]sulfinyl]-1H-thieno[3,4-d]imidazole,  
13 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-2-[(3-  
14 methoxyphenyl)methylsulfinyl]imidazolo{5,4-c}pyridine,  
15 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-2-[{2-  
16 (dimethylamino)phenyl}methylsulfinyl]-1H-benzimidazole,  
17 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-5-methoxy-2-  
18 [[[3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,  
19 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-6-methoxy-2-  
20 [[[3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,  
21 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-2-[[[(4-(3-  
22 methoxypropoxy)-3-methyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,  
23 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-5-  
24 (difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-  
25 benzimidazole,  
26 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-6-  
27 (difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-  
28 benzimidazole,

1 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-2-[[[3-methyl-4-  
2 (2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole,  
3 1-(benzotriazol-1-yl)methyl-5-methoxy-2-[[3,5-dimethyl-4-methoxy-2-  
4 pyridyl]methyl]sulfinyl]-1H-benzimidazole,  
5 1-(benzotriazol-1-yl)methyl-6-methoxy-2-[[3,5-dimethyl-4-methoxy-2-  
6 pyridyl]methyl]sulfinyl]-1H-benzimidazole,  
7 1-(benzotriazol-1-yl)methyl-2-[[4-(3-methoxypropoxy)-3-methyl-2-  
8 pyridyl]methyl]sulfinyl]-1H-benzimidazole,  
9 diethyl [5-methoxy-2-[[3,5-dimethyl-4-methoxy-2-  
10 pyridyl]methyl]sulfinyl]benzimidazol-1-yl]phosphate,  
11 1-(4-acetaminobenzenesulfonyl)-5-methoxy-2-[[3,5-dimethyl-4-methoxy-2-  
12 pyridyl]methyl]sulfinyl]-1H-benzimidazole,  
13 1-(4-acetaminobenzenesulfonyl)-6-methoxy-2-[[3,5-dimethyl-4-methoxy-2-  
14 pyridyl]methyl]sulfinyl]-1H-benzimidazole,

15 The compounds of the invention wherein the  $R_{15}$  group is an  
16 arylsulfonyl group, can be prepared by the reacting the 2-  
17 pyridylmethylsulfinyl-1H-benzimidazole derivatives (or structurally related  
18 compounds) having a free NH group within the imidazole moiety, with an  
19 arylsulfonyl chloride. In the broad sense the benzimidazole or structurally  
20 related compound which is the starting material having the free NH group, can  
21 be described by **Formula 1** wherein the  $R_{15}$  group would be H. Similarly, in  
22 the broad sense the arylsulfonyl chloride reagent is described by the formula  
23  $R_{21}(R_{17})SO_2Cl$  where the  $R_{21}$  and  $R_{17}$  groups are defined as in connection with  
24 **Formula 1. Reaction Scheme 1** discloses a process for preparing exemplary  
25 preferred compounds of the invention by reacting the 2-pyridylmethylsulfinyl-  
26 1H-benzimidazole derivative of **Formula 13** with a benzenesulfonyl chloride  
27 derivative of **Formula 14** in the presence of a suitable base. The reaction is  
28 typically conducted in an inert organic solvent, such as dichloromethane in the

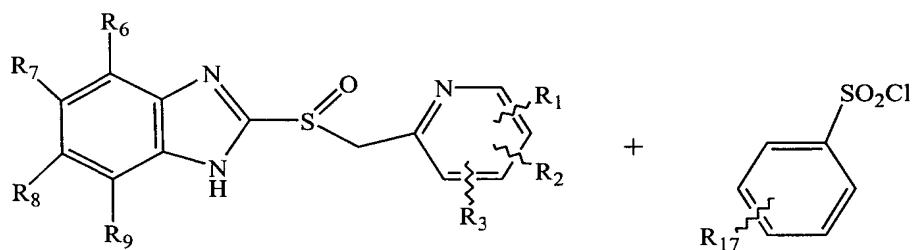
1 presence of an organic base, such as triethylamine. For compounds of  
2 **Formula 13** and **Formula 14** the  $R_1 - R_3$ ,  $R_6 - R_9$  and  $R_{17}$  groups are defined  
3 as in connection with **Formula 1**. As it can be seen in **Reaction Scheme 1**,  
4 the benzenesulfonylation reaction may give rise to two isomeric or  
5 tautomeric products depending on the nature and positions of the  $R_6 - R_9$   
6 substituents on the benzimidazole ring. The two isomeric products (which  
7 may be merely taumers) are shown in **Formulas 15** and **16**.

8 The benzenesulfonyl chloride derivatives of **Formula 14** can be  
9 obtained in accordance with procedures well known in the art.

10 Those skilled in the art will recognize the 2-pyridylmethylsulfinyl-1H-  
11 benzimidazole derivatives of **Formula 13** as the proton pump inhibitors  
12 generally known in the art and described for example in United States Patent  
13 No. 4,686,230 (*Rainer et. al.*) and in published international application WO  
14 97/48380 (*Astra Aktiobiolog*). Starting materials within the scope of **Formula**  
15 **13** include the known drugs LANSOPRAZOLE (United States Patent No.  
16 4,628,098), OMEPRAZOLE (United States Patent Nos. 4,255,431 and  
17 4,255,431), PANTOPRAZOLE (United States Patent No. 4,758,579) and  
18 RABEPRAZOLE (United States Patent No. 5,045,552) Thus, the starting  
19 compounds of **Formula 13** can be prepared in accordance with the state-of-  
20 the-art, for example as described in United States Patent Nos. 4,686,230,  
21 4,628,098, 4,255,431, 4,758,579, 5,045,552, international application WO  
22 97/48380, Journal of Medicinal Chemistry, 32, 1970-1977 (1989), Chem.  
23 Pharm. Bull. 38, 2853-2858 (1990), J. Med. Chem., 34, 1049-1062 (1991),  
24 Journal of Medicinal Chemistry, 35, 1049-1057 (1992), and Journal of  
25 Medicinal Chemistry, 35, 438-450 (1992), all of which are specifically  
26 incorporated herein by reference.

27 Although this is not shown in the reaction scheme, to obtain compounds  
28 of the invention where with reference to **Formula 1**  $R_{15}$  is  $R_{21}(C_6H_4)SO_2$  and

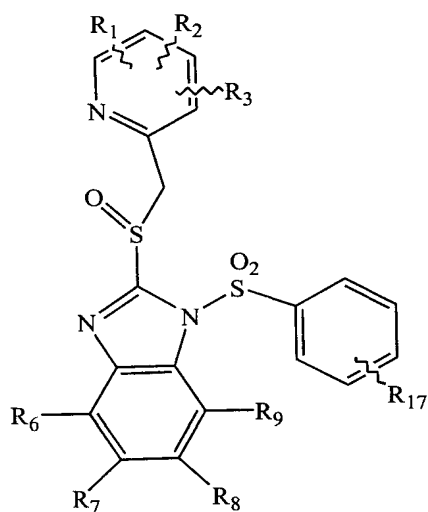
- 1 Y is  $=NR_{16}$ , a reagent of the formula  $R_{21}(C_6H_4)S(O)(Cl)NR_{16}$  is used instead  
2 of the reagent of **Formula 14**, to react with the compounds of **Formula 13**.  
3 The reagent of the formula  $R_{21}(C_6H_4)S(O)(Cl)NR_{16}$  can be obtained in  
4 accordance with methods known in the art, for example as described in the  
5 treatise COMPREHENSIVE ORGANIC FUNCTIONAL GROUP  
6 TRANSFORMATIONS, Volume 7, Editors-in-Chief A. R. Katritzky, O.  
7 Meth-Cohn and C. W. Rees (Pergamon).



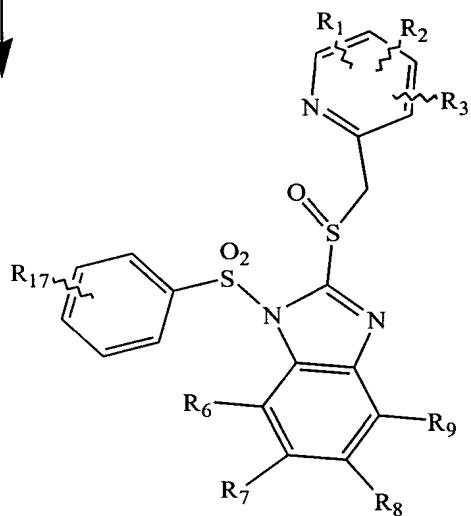
Formula 13

Formula 14

BASE



Formula 15



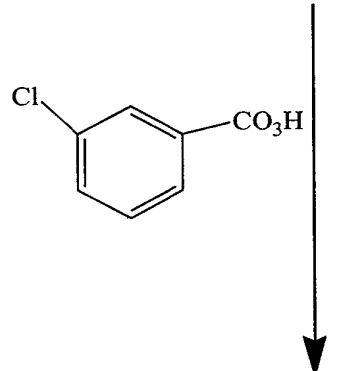
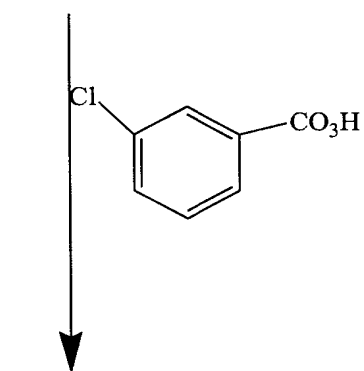
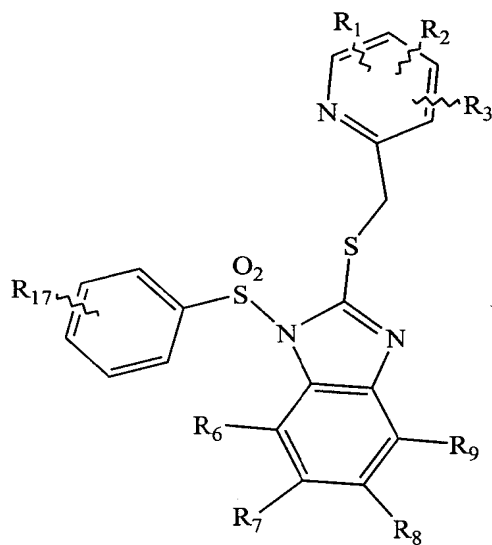
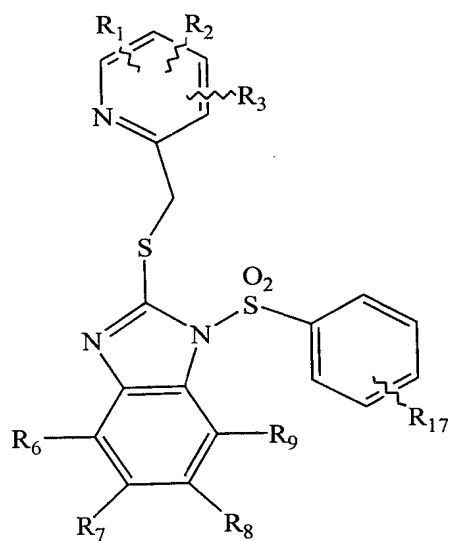
Formula 16

Reaction Scheme 1



1           Instead of using the free benzimidazole compounds of **Formula 13**,  
2   their suitable salts such as the sodium, potassium, magnesium (and other) salts  
3   can be reacted with the benzenesulfonyl chloride derivative of **Formula 13**, to  
4   also provide the exemplary compounds of the invention in accordance with  
5   **Formulas 15 and 16**.

6           **Reaction Scheme 2** discloses an alternative method for preparing the  
7   exemplary compounds of the invention, shown in **Formulas 15 and 16**. This  
8   reaction involves the oxidation of the corresponding 1-(*N*)-benzenesulfonyl-  
9   benzimidazolyl, 2-pyridylmethyl sulfide compounds of **Formulas 17 and 18** to  
10   the corresponding sulfoxides. Those skilled in the art will recognize that  
11   **Formulas 17 and 18** represent isomeric compounds which may be different or  
12   identical (tautomeric) with one another depending on the nature and position  
13   of the **R<sub>6</sub> - R<sub>9</sub>** substituents. The oxidation reaction can be performed with  
14   oxidizing agents known in the art for forming sulfoxides, for example  
15   hydrogen peroxide, *m*-chloroperoxybenzoic acid and iodosobenzene may serve  
16   for this purpose. The oxidation reaction is normally conducted in an aprotic  
17   neutral solvent, such as dichloromethane. The sulfide compounds of  
18   **Formulas 17 and 18** can be obtained by performing a benzenesulphonylation  
19   reaction (in analogy to the reaction of **Scheme 1**) on the sulfide compounds  
20   having a free benzimidazole NH group, or their suitable salt. The latter  
21   sulfides (**Formulas 17 and 18**) can be obtained in accordance with the state-  
22   of-the-art.



Reaction Scheme 2

1           The compounds of the invention where the physiologically labile  $R_{15}$   
2   group is  $R_{16}(R_{17})SO$  (sulfinyl), as defined in connection with **Formula 1**, can  
3   be made in reactions which are analogous to the reactions shown in **Scheme 1**,  
4   except that instead of an arylsulfonyl chloride an arylsulfinyl chloride of  
5   formula  $R_{16}(R_{17})SOCl$  is used. The arylsulfinylation reaction is usually  
6   conducted in the presence of an organic base, in a solvent such as dioxane,  
7   tetrahydrofuran, or an alcohol. The arylsulfinyl chloride of formula  
8    $R_{16}(R_{17})SOCl$  can be made from the corresponding sulfinic acid or salt having  
9   the formula  $R_{16}(R_{17})SO_2Na$ , by treatment with thionyl chloride. In view of  
10   their close analogy to the sulfonylation reactions of **Scheme 1**, the  
11   sulfinylation reactions are not shown in a scheme.

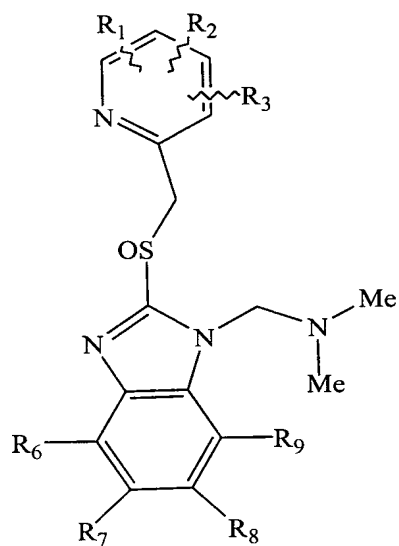
12           The compounds of the invention where the physiologically labile  $R_{15}$   
13   group together with the 2-pyridylmethylsulfinyl-1H-benzimidazole derivatives  
14   (or structurally related compounds) form a *Mannich* base, can be made under  
15   conditions which are generally applicable and known in the art for forming  
16   *Mannich* bases. A specific detailed description for forming *Mannich* base  
17   type prodrugs is provided by *Bundgaard et al.* in **Methods in Enzymology**  
18   **112**, p347 -359 which is incorporated herein by reference. Generally  
19   speaking, the preparation of *Mannich* base type prodrugs of this invention  
20   involves heating a mixture of an amine of the formula  $R_{19}R_{20}NH$  with an  
21   aldehyde or ketone of the formula  $OC(R_{18})_2$  in an alcohol, water, dioxane or  
22   other suitable solvent. The symbols  $R_{18} - R_{20}$  are defined as in connection  
23   with **Formula 1**.

24           **Reaction Scheme 3** illustrates the preparation of exemplary *Mannich*  
25   base type compounds of the invention from the 2-pyridylmethylsulfinyl-1H-  
26   benzimidazole derivatives of **Formula 13** using formaldehyde as the aldehyde  
27   and dimethylamine as the amine. As it can be seen in the reaction scheme, this  
28   reaction also may provide two isomeric products of **Formula 19** and **20**,

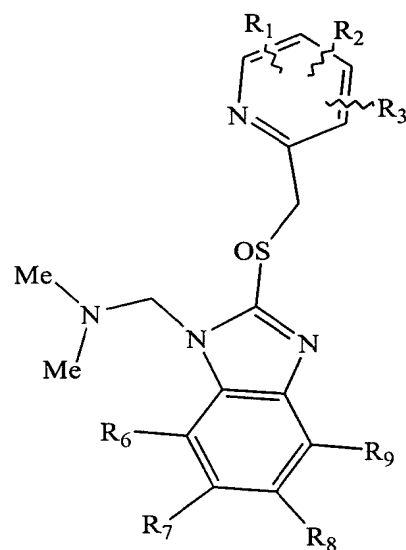
1 respectively. The two products may be identical (tautomeric) depending on  
2 the nature and position of the  $R_6$  -  $R_9$  substituents.

Formula 13

$\text{CH}_2\text{O}$ ,  
 $\text{HN}(\text{Me})_2$ ,  
 $\text{MeOH}$ , heat



Formula 19



Formula 20

Reaction Scheme 3

1           The compounds of **Formula 19** and **Formula 20** can be and preferably  
2 are prepared by an alternative method including a reaction of N-halomethyl  
3 dialkylamines with a sodium salt of **Formula 13**, or a tetraammonium salt of  
4 **Formula 13**, or with a compound of **Formula 13** in the presence of sodium  
5 tert-butoxide. N-chloromethyl dialkylamines were prepared as described by  
6 *Boehme et al.*, (Chemische Berichte, vol., 93, pp1305-1309 (1960) and  
7 Chemische Berichte, vol., 95, pp 1849-1858(1962)), and a  
8 tetra(alkyl)ammonium salt of **Formula 13** was prepared by a method  
9 described in United States Patent No. 5,021,433. For example,  
10 tetrabutylammonium salt of 2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]  
11 sulfinyl]-5-methoxy-1H-benzimidazole was prepared as described in the  
12 United States Patent No. 5,021,433 and used *in situ*. Tetrabutylammonium salt  
13 of 2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-5-methoxy-1H-  
14 benzimidazole was reacted with 1-chloromethyl-N,N-dimethylamine in  
15 dichloromethane to give a mixture of 1-(N,N-dimethylamino)methyl-2-[[[(3,5-  
16 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-5-methoxy-1H-benzimidazole  
17 and 1-(N,N-dimethylamino)methyl-2-[[[(3,5-dimethyl-4-methoxy-2-  
18 pyridyl)methyl]sulfinyl]-6-methoxy-1H-benzimidazole. 1-(Heteroaryl-N-  
19 methyl)-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-(5 and 6-  
20 methoxy)-1H-benzimidazole was synthesized by a similar method. For  
21 example, a mixture of 1-(benzotriazol-1-yl)methyl-2-[[[(3,5-dimethyl-4-  
22 methoxy-2-pyridyl)methyl]sulfinyl]-5-methoxy-1H-benzimidazole and 1-  
23 (benzotriazol-1-yl)methyl-2-[[[(3,5-dimethyl-4-methoxy-2-  
24 pyridyl)methyl]sulfinyl]-6-methoxy-1H-benzimidazole was prepared by a  
25 reaction of sodium salt of 2-[[[(3,5-dimethyl-4-methoxy-2-  
26 pyridyl)methyl]sulfinyl]-5-methoxy-1H-benzimidazole with 1-chloromethyl-  
27 1H-benzotriazole.

28           Another method for preparing the compounds of **Formula 19** and

1   **Formula 20** is using a reaction of 1-chloromethyl-2-[(2-  
2   pyridyl)methylsulfinyl]-1H-benzimidazole compounds with dialkylamines  
3   such as morpholine, dimethylamine, pyrrolidine, and piperidine. 1-  
4   Chloromethyl-2-[(2-pyridyl)methylsulfinyl]-1H-benzimidazole compounds  
5   were prepared by a method described in European Pat., No. 279,149 (*Alminger*  
6   *et al.*). For example, a mixture of 1-chloromethyl-5-methoxy-2-[[4-methoxy-  
7   3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-  
8   chloromethyl-6-methoxy-2-[[4-methoxy-3,5-dimethyl-2-  
9   pyridyl)methyl]sulfinyl]-1H-benzimidazole was reacted with morpholine to  
10   give a mixture of 1-(morpholin-4-yl)methyl-5-methoxy-2-[[4-methoxy-3,5-  
11   dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(morpholin-4-  
12   yl)methyl-6-methoxy-2-[[4-methoxy-3,5-dimethyl-2-  
13   pyridyl)methyl]sulfinyl]-1H-benzimidazole.

14           A significant advantage of the compounds of the present invention is  
15   that they can release the active forms of the proton pump inhibitors  
16   spontaneously by hydrolysis in the mammalian (including human) body.  
17   Hydrolysis can occur chemically or enzymatically. Because the compounds of  
18   this invention spontaneously release the active form of the proton pump  
19   inhibitor drugs by *in vivo* hydrolysis, they can attain longer duration of  
20   effective drug concentration in the body. Thus, the compounds of the present  
21   invention are prodrugs which are converted to active drugs by hydrolysis in  
22   the body, providing long duration of effective concentration. The long duration  
23   of inhibitory activity by spontaneous hydrolysis of the compounds of this  
24   invention allows more effective inhibition of gastric acid secretion, which  
25   enables better therapy of acid related disease as defined on p.1. and p.2.  
26   Compounds of this invention can be administered for inhibiting gastric acid  
27   secretion orally. The typical daily dose of the compounds will depend on  
28   various factors such as the individual requirement of each patient. In general,

1 oral and parenteral dosages will be in the range of 5 to 100 mg per day.

2 Those skilled in the art will readily understand that for oral  
3 administration the compounds of the invention are admixed with  
4 pharmaceutically acceptable excipients which *per se* are well known in the art.  
5 Specifically, a drug to be administered systemically, it may be conected as a  
6 powder, pill, tablet or the like or as a syrup or elixir suitable for oral  
7 administration. Description of the substances normally used to prepare tablets,  
8 powders, pills, syrups and elixirs can be found in several books and treatise  
9 well known in the art, for example in Remington's Pharmaceutical Science,  
10 Edition 17, Mack Publishing Company, Easton, Pennsylvania.

11 Compounds of the present invention can be combined with certain  
12 amounts of known proton pump inhibitors, *e. g.* LANSOPRAZOLE,  
13 OMEPRAZOLE, PANTOPRAZOLE, or RABEPRAZOLE, to provide a  
14 drug-prodrug combination, and the combination administered for inhibition of  
15 gastric acid secretion. Thus, initially the proton pump inhibitor (drug) inhibits  
16 gastric acid secretion of the patient. The aforesaid known and widely used  
17 proton pump inhibitors have 60-90 minutes of plasma half-life. As the  
18 effective concentration of the proton pump inhibitor (drug) is decreased by  
19 metabolism, the compounds of the present invention (prodrug) continuously  
20 undergoes hydrolysis and provides and maintains new active inhibitor  
21 concentration in the mammalian, including human body.

22 A disadvantage of the presently used proton pump inhibitors is that for  
23 therapy by injection in a liquid form they must be reconstituted from a  
24 lyophilized powder in a medium having the high pH of approximately 9.5.  
25 The prodrugs of the present invention overcome the disadvantage of requiring  
26 a reconstituting medium having such high pH, because the compounds of the  
27 present invention can be reconstituted to form an injectable liquid in a medium  
28 of approximately pH 6.0 to 8.5. It will be readily appreciated by those skilled

1 in the art that for administration in liquid form by injection the liquid that  
2 reconstitutes the drug is a pharmaceutically acceptable aqueous solution that  
3 *per se* is known in the art. Such pharmaceutically acceptable solutions utilized  
4 for administration of drugs in injectable form are described for example in the  
5 treatise PHARMACEUTICAL DOSAGE FORMS (Parenteral Medications,  
6 Volume 1, Edited by K. E. Avis, H. A. Lieberman and L. Lachman (1992).

7       Among the benefits of the pre-proton pump inhibitor (P-PPI) type of  
8 drugs of the present invention is their ability to provide more effective  
9 treatment of erosive esophagitis and of less severe reflux diseases as well.  
10 This is because effective treatment of erosive esophagitis (and to a lesser  
11 extent of lesser reflux diseases) requires prevention of the reflux of gastric  
12 contents at pH 3.0 or still lower pH. The current PPI drugs allow several  
13 acidic excursions to pH < 2.0 per day, resulting in a moderate to weak  
14 amelioration of symptoms. However, healing would require elevation to pH  
15 > 4.0 for about 16 hours per day or longer. When, as in current usual  
16 treatment by PPIs, the other 8 hours contain episodic acidity to pH 3.0 or less,  
17 the patients tend to continue to complain of pain. The more effective and  
18 more continues acid suppression by the drugs of the present invention is likely  
19 to result in substantially better treatment of this disease, as well as faster  
20 healing of all acid related erosions or ulcers.

21       The pre-proton pump inhibitor (P-PPI) type of drugs of the present  
22 invention provide improved dual therapy for *H. pylori* eradication. This is  
23 because the PPI's synergize with cell division dependent antibiotics such as  
24 amoxicillin (cell wall biosynthesis) and clarithromycin (protein synthesis) by  
25 elevating gastric surface pH to enable a larger fraction of the bacterial  
26 population to be in dividing phase during presentation of the antibiotic to the  
27 gastric lumen. However, their effect on intragastric pH is limited by their  
28 dwell time in the plasma. The pre-proton pump inhibitor (P-PPI) type of drugs



1 of the present invention can continuously elevate intragastric pH close to  
2 neutrality on current once a day therapy. Therefore, 100% eradication of the  
3 bacteria is expected in dual therapy with the prodrugs of the invention (for  
4 example a pro-drug of OMEPRAZOLE in accordance with the invention) plus  
5 an effective antibiotic, such as amoxicillin.

6 Even monotherapy for *H. pylori* eradication is likely to be successful  
7 with the pre-proton pump inhibitor (P-PPI) type of drugs of the present  
8 invention. This is because in the absence of acid, the enzyme *H. pylori* urease  
9 elevates environmental pH to > 8.3, which is toxic to the organism. PPI's in  
10 current formulation inhibit growth or present of the organism in the antrum,  
11 due to elevation of antral pH to close to neutrality. Elevation of 24 hour pH to  
12 neutrality, as it can be accomplished with the drugs of the present invention, is  
13 likely to result in "self eradication" of the bacteria.

14 Approximately 30% of patients with gastrointestinal distress appear  
15 with symptoms without quantitative underlying disease (non-ulcer dyspepsia).  
16 The most likely cause for these symptoms is upper gastrointestinal afferent  
17 nerve sensitivity to gastric acid. Only acid ablation ameliorates these  
18 symptoms and this can be attained with the drugs of the present invention.

19 By way of concrete examples, the following tests and results are  
20 described. Certain compounds of the invention have been tested in one or  
21 more standard laboratory tests that demonstrate gastric antisecretory activity.  
22 The compounds of the invention did not directly inhibit the  $K^+$ -dependent  
23 ATP hydrolysis of gastric H,K-ATPase. However, after hydrolysis the  
24 compounds of this invention showed strong inhibition of gastric H,K-ATPase  
25 activity. This is consistent with the knowledge that the compounds obtained  
26 by hydrolysis *e. g.* LANSOPRAZOLE, OMEPRAZOLE, PANTOPRAZOLE  
27 and RABEPRAZOLE are well known H,K-ATPase inhibitors. For example,  
28 1-benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-

1 pyridyl)methylsulfinyl]-1H-benzimidazole was tested for inhibitory activity of  
2 gastric H,K-ATPase. Initially this compound did not inhibit gastric H,K-  
3 ATPase. However, gastric H,K-ATPase activity was spontaneously inhibited  
4 as hydrolysis of this compound in aqueous solution at pH 7.4 proceeded. After  
5 5.75 hr -hydrolysis at pH 7.4, this compound inhibited 91% of gastric H,K-  
6 ATPase activity, same as 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
7 pyridyl)methylsulfinyl]-1H-benzimidazole (OMEPRAZOLE) which was the  
8 product of the hydrolysis. It was determined that 1-benzenesulfonyl-5-  
9 methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-  
10 benzimidazole was hydrolyzed to 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
11 pyridyl)methylsulfinyl]-1H-benzimidazole (OMEPRAZOLE) with a half-life  
12 ( $t_{1/2}$ )  $3 \pm 0.5$  hr at 37 °C at pH 7.4.

13       When a mixture of 2-{4-[(5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
14 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-  
15 pyridyl)acetamide and 2-{4-[(6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
16 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-  
17 pyridyl)acetamide was orally administrated to male rat, 5-methoxy-2-[(3,5-  
18 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole  
19 (OMEPRAZOLE) was continuously released to the plasma for more than 4  
20 hours as a result of the hydrolysis of 2-{4-[(5-methoxy-2-[(3,5-dimethyl-4-  
21 methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-  
22 (2-pyridyl)acetamide and 2-{4-[(6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
23 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-  
24 pyridyl)acetamide. As a control experiment, when OMEPRAZOLE was  
25 administrated to male rat, OMEPRAZOLE Has completely disapperead from  
26 the plasma within 1.5 hr. Bioavailability of 2-{4-[(5-methoxy-2-[(3,5-  
27 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-  
28 yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide was much higher than that of

1 OMEPRAZOLE after oral administration.

2       When a mixture of 2-{4-[(5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
3 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-  
4 pyridyl)acetamide and 2-{4-[(6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
5 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-  
6 pyridyl)acetamide was orally administered to male rat, gastric acid secretion  
7 was significantly and continuously inhibited. After 5 hours of oral  
8 administration, a mixture of 2-{4-[(5-methoxy-2-[(3,5-dimethyl-4-methoxy-  
9 2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-  
10 pyridyl)acetamide and 2-{4-[(6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
11 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-  
12 pyridyl)acetamide provided maximum 90% of inhibition of gastric acid  
13 secretion stimulated by histamine, while OMEPRAZOLE provided only about  
14 45% of inhibition. There is a report that 50-60% of inhibition of gastric acid  
15 output is obtained after 4 to 6 hours of intravenous administration of  
16 OMEPRAZOLE (*Katashima, et al.*, Drug metabolism and Disposition, vol.,  
17 23, 718-723, 1995). Probably, lower inhibition (45 %) of gastric acid  
18 production after administration of OMEPRAZOLE in this experiment,  
19 compared to the reported data (50-60 %) obtained by Katashima. et al, is due  
20 to the different method of administration. However, it is well known that oral  
21 potency of OMEPRAZOLE without enteric-coating is significantly lower than  
22 that found after i.v. or i.d. administration in both rat and dog (*Larsson et al.*,  
23 Scand. J. Gastroenterology, vol. 20 (suppl. 108), 23-35, 1985). The  
24 compounds of this invention do not need enteric-coating for protection from  
25 acid-catalyzed decomposition. Furthermore, the compounds of this invention  
26 provide continuous inhibition of gastric acid secretion. Maximum inhibition  
27 by the compound of 2-{4-[(5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
28 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-

1 pyridyl)acetamide and 2- {4-[(6-methoxy-2- {[(3,5-dimethyl-4-methoxy-2-  
2 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} -N-(2-  
3 pyridyl)acetamide obtained after 5 hours shows that the compounds of the  
4 invention are continuously converted to the corresponding PPI in vivo, which  
5 inhibits gastric acid secretion.

## 6 SPECIFIC EMBODIMENTS AND EXPERIMENTAL 7 DESCRIPTION

### 8 Preparation of Intermediates

9 Reference Example 1: Preparation of [(morpholin-4-yl)alkoxy]benzene-4-  
10 sulfonyl chloride

11 [(morpholin-4-yl) alkoxy] benzene-4-sulfonyl chloride was prepared by  
12 chlorosulfonylation of 4-[(phenoxy)alkoxy]morpholine using chlorosulfonic  
13 acid in the presence of dichloromethane or chloroform. In this reaction,  
14 chloroform or dichloromethane was important to avoid the cleavage of ether  
15 linkage of alkoxybenzene moiety by chlorosulfonic acid.

16 [3-(Morpholin-4-yl) propoxy] benzene-4-sulfonyl chloride was prepared by  
17 chlorosulfonylation of 4-(3-phenoxypropyl)morpholine using chlorosulfonic  
18 acid in the presence of dichloromethane or chloroform. For example, to a  
19 solution of 2.2 g (10 mmole) of N-(3-phenoxypropyl) morpholine in 20 ml of  
20 chloroform, 2 ml of chlorosulfonic acid (30 mmole) was slowly added at -10  
21 °C and stirred for 30 min. The reaction mixture was stirred at room  
22 temperature for 5 hr. Chloroform was removed from lower layer. Lower layer  
23 was treated with chopped-ice to give solids. To a mixture of ice and solid  
24 product, 10 g of sodium phosphate (tribasic) was added and stirred with  
25 cooling. Chlorosulfonyl compound was extracted with dichloromethane (300  
26 ml). Dichloromethane extract was dried over anhydrous magnesium sulfate  
27 and evaporated under reduced pressure. 1.6 g of [3-(morpholin-4-yl) propoxy]  
28 benzene-4-sulfonyl chloride was obtained.

1 [2-(Morpholin-4-yl)ethoxy]benzene-4-sulfonyl chloride was prepared using N-  
2 (2-phenoxyethyl) morpholine by similar reaction described above. For  
3 example, 7.2 g of N-(2-phenoxyethyl)morpholine HCl salt was resuspended in  
4 20 ml of dichloromethane and 7 ml of chlorosulfonic acid was slowly  
5 introduced with cooling by ice-jacket. The reaction mixture was stirred at 0 °C  
6 for 2 hr, then, at room temperature overnight. Dichloromethane (350 ml) was  
7 added to the reaction mixture and excess chlorosulfonic acid was destroyed by  
8 adding icy water(about 100 g). Aqueous layer was adjusted to pH 8.5 by  
9 concentrated sodium carbonate solution with cooling by ice. Dichloromethane  
10 was dried over anhydrous magnesium sulfate and evaporated under reduced  
11 pressure to give 8.1 g of [2-(morpholin-4-yl)ethoxy]benzene-4-sulfonyl  
12 chloride. M.P. 48-50 °C.

13 N-(2-Phenoxyethyl) morpholine was prepared by a modified method of Grail.  
14 et al (Journal of American Chemical Society, 1952, 74, 1313-1315). For  
15 example, 9.2 g of phenol and 18.6 g of N-(2-chloroethyl)morpholine HCl salt  
16 were dissolved in 120 ml of isopropanol and 12 g of potassium hydroxide was  
17 added with cooling. The reaction mixture was refluxed for 12 hours. Solid  
18 (KCl) was filtered off. The filtrate was distilled off. The residual material was  
19 treated with 150 ml of 1 N NaOH, then, extracted with dichloromethane (200  
20 ml). Dichloromethane layer was again washed with a solution of 0.1 N sodium  
21 carbonate in 10% NaCl solution. Dichloromethane layer was dried over  
22 anhydrous magnesium chloride, and evaporated under reduced pressure.  
23 Residual syrup was dissolved in 100 ml of 1.5 N HCl solution, and washed  
24 with 100 ml of chloroform. Aqueous layer was treated with 100 ml of toluene  
25 and water was removed by Dean-Stark apparatus by distillation. Residual  
26 toluene layer was cooled to give crystalline solid, which was collected by  
27 filtration. 12 g of N-[(2-phenoxy)ethyl]morpholine HCl salt (50% yield )was  
28 obtained.

1 N-[3-(Phenoxy)propyl] morpholine was prepared by a reaction of 3-  
2 (phenoxy)propyl bromide with morpholine. For example, 3-(phenoxy)propyl  
3 bromide (7.8 ml, 50 mmole) was added to morpholine (8 ml) in toluene (50  
4 ml) and refluxed overnight. NaOH solution (2 g of NaOH in 20 ml of water)  
5 was added and additionally refluxed for 4 hr. Toluene was removed by  
6 distillation under reduced pressure. Residue was treated with  
7 dichloromethane(200 ml) and water(200 ml). Dichloromethane layer was dried  
8 and concentrated. Residue was treated with dichloromethane-heptane to give 7  
9 g of 4-[3-(phenoxy)propyl] morpholine.

10 [2-{2-(Morpholin-4-yl)ethoxy}ethoxy]benzene-4-sulfonyl chloride was  
11 prepared using 4-[2-[2-(phenoxy)ethoxy]ethyl]morpholine by a similar  
12 reaction described above. For example, 2-(phenoxy)ethanol (4.0 ml) was  
13 added to 5.4 g of N-(2-chloroethyl)morpholine hydrochloride and 6 g of  
14 sodium tert-butoxide in 70 ml of toluene. The reaction mixture was refluxed  
15 for 16 hr. EtOAc (100 ml) was added and washed with water (200 ml).  
16 Organic layer was separated, and again, extracted with 0.5 N HCl solution  
17 (120 ml). Aqueous layer was washed again with chloroform (30 ml), then, was  
18 adjusted to pH 10.5 by adding NaOH solution. The product, [2-[2-(morpholin-  
19 4-yl)ethoxy]ethoxy]benzene, was extracted with dichloromethane (200 ml)  
20 from water. Organic layer was again washed with water, dried over anhydrous  
21 magnesium sulfate, and concentrated under reduced pressure. The product, [2-  
22 [2-(morpholin-4-yl)ethoxy]ethoxy]benzene, was obtained as a yellow syrup  
23 (5.4 g). TLC analysis showed over 99% purity and the structure was confirmed  
24 by NMR. The syrupy product was used in situ for preparing [2-{2-(morpholin-  
25 4-yl)ethoxy}ethoxy]benzene-4-sulfonyl chloride.

26 5.0 g of 2-[2-(morpholin-4-yl)ethoxy]ethoxybenzene was dissolved in 70 ml  
27 of dichloromethane. In ice bath, chlorosulfonic acid (7 ml) was slowly added.  
28 The reaction mixture was stirred at room temperature overnight. Two layers

1 were separated. Chloroform layer, upper layer, was removed. Pale brown  
2 syrup, lower layer, was added to 100 g of chopped ice. Dichloromethane (200  
3 ml) was added, and concentrated sodium carbonate solution was slowly added  
4 upto pH 9 under 4 °C with good stirring. Dichloromethane layer was  
5 separated, dried over anhydrous magnesium sulfate, and evaporated under  
6 reduced pressure. Yellow syrup was obtained, which was dried in vacuo. 3.8 g  
7 of [2-{2-(morpholin-4-yl)ethoxy}ethoxy]benzene-4-sulfonyl chloride was  
8 obtained.

9 Reference Example 2: Preparation of [2-(dimethylamino)ethoxy]phenyl-4-  
10 sulfonyl chloride

11 2 g of N,N-dimethyl-N-[(2-phenoxy)ethyl]amine was dissolved in 10 ml of  
12 dichloromethane and 3 ml of chlorosulfonic acid was slowly added under ice  
13 cooling. The mixture was stirred at room temperature for 3 hr and poured into  
14 ice. Dichloromethane (100 ml) was added and aqueous layer was neutralized  
15 by concentrated sodium carbonate solution with keeping temperature under 4  
16 °C. Dichloromethane layer was dried over anhydrous magnesium sulfate and  
17 evaporated under reduced pressure. 0.8 g of [2-  
18 (dimethylamino)ethoxy]phenyl-4-sulfonyl chloride was obtained.

19 Reference Example 3: Preparation of N-[4-(chlorosulfonyl)phenyl]urea  
20 N-[4-(chlorosulfonyl)phenyl]urea was prepared by a known method (R. J. W.  
21 Cremlyn, D. Leonard, and R. Motwani (1973) J. Chem. Soc., Perkin I 500-  
22 503).

23 Chlorosulfonic acid (4.4 ml) was added to phenylurea (2.7 g) in an ice bath,  
24 then, warmed to 60 °C for 3 hr. The syrup was poured on chopped ice with  
25 good mixing. Solid was separated and dried in vacuo. 2.3 g of product was  
26 obtained. M.P. 138-141 °C.

27 Reference Example 4: Preparation of N-[(p-chlorosulfonyl)phenyl]morpholine  
28 N-[(p-Chlorosulfonyl)phenyl] morpholine was synthesized by a modified

1 method of Cremlyn, et al. (R. J. Cremlyn, J. P. Bassin, S. Farouk, M.  
2 Potterton, and T. Mattu. (1992) Phosphorus, Sulfur, and Silicon, Vol., 73, pp.  
3 107-120).  
4 10 g of 4-phenyl morpholine in 50 ml of chloroform was added to 25 ml of  
5 chlorosulfonic acid in a ice-jacket. The reaction mixture was stirred at reflux  
6 for 7 hr. Brown syrup was poured into dichloromethane (150 ml) and chopped  
7 ice (100 g) with stirring, and neutralized by saturated sodium phosphate,  
8 tribasic, with ice-cooling. Collect dichloromethane layer, dried over anhydrous  
9 magnesium sulfate. Organic solvent was evaporated under reduced pressure to  
10 give yellow solid, which was dried in vacuo. 6.1 g of product was obtained. M.  
11 P. 154-156 °C.

12 Reference Example 5: Preparation of pyridine-3-sulfonyl chloride

13 Pyridine-3-sulfonyl chloride was prepared by a method of Alo, et al. (B. I.  
14 Alo, O. B. Familoni, F. Marsais, and G. Queguiner, (1992) Journal of  
15 Heterocyclic Chemistry, vol. 29, pp 61-64.)  
16 24 g of phosphorus pentachloride was added to a suspension of 15 g of  
17 pyridine-3-sulfonic acid in 30 ml of phosphorus oxychloride and heated at 120  
18 °C for 12 hr. The reaction mixture was concentrated by distillation under  
19 reduced pressure, and treated with toluene. Solid obtained was collected and  
20 dried in vacuo. 16.7 g of product was obtained. M. P. 138-141 °C

21 Reference Example 6: Preparation of m-(chlorosulfonyl)benzo-15-crown-5-  
22 ether

23 To an ice-cold solution of benzo-15-crown-5-ether (536.6 mg, 2 mmole) in 5  
24 ml of chloroform and cooled in ice-bath, 0.3 ml of chlorosulfonic acid (4.5  
25 mmole) was slowly added. The reaction mixture was stirred in ice bath for 2  
26 hr, then, 5 hr at room temperature. The reaction mixture was added to chopped  
27 ice and extracted with dichloromethane (50 ml). Combined organic layer was  
28 dried over magnesium chloride, and evaporated. 374 mg of product was



1 obtained. M.P. 79-84 °C

2 m-(Chlorosulfonyl)benzo-18-crown-6-ether was prepared using same method

3 as described above. Yield was about 46%. M. P. 108-110 °C

4 Reference Example 7: Preparation of 2-[p-(chlorosulfonyl)phenoxy]-N-(2-

5 pyridyl)acetamide

6 1.32 g of 2-(phenoxyacetyl)aminopyridine HCl salt (5 mmole) was

7 resuspended in 10 ml of dichloromethane and 2 ml of chlorosulfonic acid was

8 added in ice-bath to give clear solution. The solution was stirred at room

9 temperature for 3 hr. The reaction mixture was added to ice-water with good

10 stirring to give white solids. The solids were filtered, washed with acetonitrile,

11 and dried in vacuo. 0.65 g of solid was obtained. M. P. 170-175 °C

12 (decomposition)

13 Reference Example 8: Preparation of N-[p-(chlorosulfonyl)phenylmethyl]-

14 N,N-dimethylamine HCl salt

15 1.5 ml of N,N-dimethylbenzylamine (10 mmole) was dissolved in 6 ml of

16 dichloromethane and 2 ml of chlorosulfonic acid was added in ice bath

17 cooling. The reaction mixture was warmed to 40 °C for 40 min, and stirred at

18 room temperature for 1 hr. The reaction mixture was concentrated under

19 reduced pressure and poured into ice to give solids, which were collected and

20 dried in vacuo. 1.6 g (59.2%) of N-(p-chlorosulfonylphenylmethyl)-N,N-

21 dimethylamine HCl salt was obtained.

22 Reference Example 9: Preparation of 2-[p-(chlorosulfonyl)phenoxy]acetamide

23 3.0 g of 2-(phenoxy)acetamide was dissolved in 10 ml of dichloromethane and

24 6 ml of chlorosulfonic acid was slowly added at 0 °C. The reaction mixture

25 was stirred at room temperature for 10 hr. Dichloromethane was evaporated

26 under reduced pressure. Residual material was poured on chopped ice. Solid

27 was collected by filtration and dried in vacuo. 3.9 g of product was obtained.

28 M.P. 166-171 °C (decomposition)

1 Reference Example 10: Preparation of N-(p-chlorosulfonylphenylmethyl)  
2 pyridinium chloride

3 p-(Chloromethyl)benzenesulfonyl chloride (2.2 g) was dissolved in acetonitrile  
4 (20 ml)-dichloromethane (20 ml) and pyridine (1.9 ml) was added. The  
5 reaction mixture was refluxed for 3 hr. Brown syrup was separated from  
6 solvent, and was lyophilized in vacuo. Reddish brown product (2.9 g) was  
7 obtained. M.P. 105-108 °C.

8 Reference Example 11: Preparation of p-(dimethylamino)benzenesulfonyl  
9 chloride

10 N,N-Dimethylaniline (8 ml) was dissolved in 20 ml of chloroform, and  
11 chlorosulfonic acid (20 ml) was slowly added with cooling. The reaction  
12 mixture was refluxed for 6 hr. The reaction mixture was cooled and poured on  
13 ice (100 g). Dichloromethane (120 ml) was added and aqueous layer was  
14 neutralized by concentrated sodium carbonate solution with keeping  
15 temperature below 4 °C. Organic layer was again washed with ice-cold 0.1 N  
16 sodium bicarbonate solution, and dried over anhydrous magnesium sulfate.  
17 Organic layer was concentrated under reduced pressure. Residual material was  
18 crystallized from ethyl ether-heptane to give yellowish green solid. p-  
19 (Dimethylamino)benzenesulfonyl chloride (4.2 g) was obtained. M. P. 108-  
20 111 °C

21 Reference Example 12: Preparation of N-(carbamoylmethyl)-2-[4-  
22 (chlorosulfonyl)phenoxy]acetamide

23 a) Preparation of N-(carbamoylmethyl)-2-(phenoxy)acetamide

24 Glycinamide HCl salt (5 g) was resuspended in 200 ml of dichloromethane  
25 and 14 ml of triethylamine at 4 °C. Phenoxyacetyl chloride (6 ml) was slowly  
26 added with good stirring. The reaction mixture was stirred at room temperature  
27 for 3 hr, then, refluxed for 3 hr. The reaction mixture was cooled to give  
28 crystalline solid, which was collected by filtration. Filtered solid was washed

1 with water, and dried in vacuo to give 7.5 g of product, N-(carbamoylmethyl)-  
2 2-(phenoxy)acetamide . The filtrate was washed with water, and 0.1 N sodium  
3 carbonate solution. The filtrate was concentrated, and treated with ether to  
4 give additional product, 1.2 g of N-(carbamoylmethyl)-2-(phenoxy)acetamide .  
5 M.P. 138-140 °C

6 b) Preparation of N-(carbamoylmethyl)-2-[4-  
7 (chlorosulfonyl)phenoxy]acetamide

8 N-(carbamoylmethyl)-2-(phenoxy)acetamide (2.08 g) was resuspended in 30  
9 ml of dichloromethane and chlorosulfonic acid (6 ml) was slowly added with  
10 cooling. The reaction mixture was stirred at room temperature for 2 hr. Two  
11 layers separated after standing for 10 min without stirring. Upper layer was  
12 decanted. Lower layer was poured to chopped ice (60 g) with good mixing to  
13 give white solid, which was collected by filtration and washed with ice-cold  
14 water. The solid was dried in vacuo to give 2.78 g of N-(carbamoylmethyl)-2-  
15 [4-(chlorosulfonyl)phenoxy]acetamide .  
16 M.P. 97-100 °C (decomposition)

17

#### 18 EXAMPLE 1

19 1-Benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
20 pyridyl)methylsulfinyl]-1H-benzimidazole and 1-Benzensulfonyl-6-methoxy-  
21 2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole

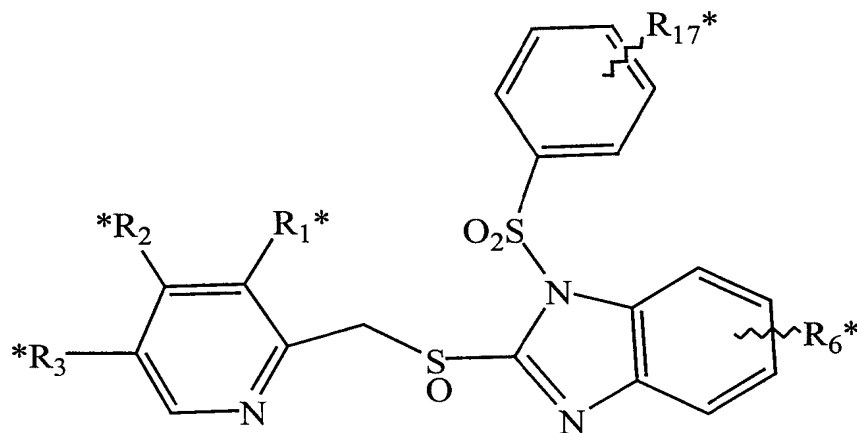
22 Method A: 5-Methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
23 pyridyl)methylsulfinyl]-1H-benzimidazole(172 mg, 0.5 mmole) was dissolved  
24 in 20 ml of dichloromethane and 0.140 ml of triethylamine. The solution was  
25 cooled to 0-4 °C in an ice bucket. Benzenesulfonyl chloride (96 mg, 0.55  
26 mmole) was slowly added and stirred at 0-4 °C with thin layer chromatography  
27 monitoring (developing solvent system: chloroform-methanol (10:1) and  
28 acetonitrile-chloroform (1:1)). After the reaction was complete, the organic

1 layer was washed with an aqueous solution composed of 0.1 M NaCl, and 0.1  
2 M sodium phosphate, pH 8.5. The organic layer was dried over anhydrous  
3 magnesium sulfate and concentrated under reduced pressure. The residual  
4 material was crystallized from dichloromethane-ethyl ether-heptane to provide  
5 127 mg of product. M. p. 87-89 °C (decomposition). Heptane was introduced  
6 to the remaining organic layer to provide a second crop of product (104 mg).  
7 After combining the solids, 231 mg of the product (yield 95%) was obtained.  
8 The product was composed of an mixture of 1-benzensulfonyl-5-methoxy-2-  
9 [(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole and 1-  
10 benzensulfonyl-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
11 pyridyl)methylsulfinyl]-1H-benzimidazole (3:2 ratio by NMR)  
12 <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ: 8.10-8.15 (m, 3H), 7.45-7.80(m, 5H), 7.0-7.1(m, 1H),  
13 4.8-5.0(2q, 2AB total 2H), 3.83 and 3.92 (2s, total 3H), 3.75(s, 3H), 2.31(s,  
14 3H), 2.23(s, 3H)  
15 Method B: A mixture of 1-benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-  
16 methoxy-2-pyridyl)methylthio]-1H-benzimidazole and 1-benzenesulfonyl-6-  
17 methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylthio]-1H-  
18 benzimidazole was prepared by reacting 5-methoxy-2-[(3,5-dimethyl-4-  
19 methoxy-2-pyridyl)methylthio]-1H-benzimidazole with benzenesulfonyl  
20 chloride as in method A. 1-Benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-  
21 methoxy-2-pyridyl)methylthio]-1H-benzimidazole was isolated by silica gel  
22 column chromatography and used in the next step as follows. 1-  
23 Benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
24 pyridyl)methylthio]-1H-benzimidazole (318 mg, 1 mmole) in 30 ml of  
25 dichloromethane was cooled to - 20 °C. A dichloromethane solution (5 ml)  
26 containing m-chloroperbenzoic acid (equivalent to 1 mmole from 60% purity)  
27 was slowly added. The reaction was monitored by thin layer chromatography.  
28 After 5 hours the organic layer was washed with an aqueous solution of 0.1 M

1 sodium bicarbonate and 50 mM sodium thiosulfate. The organic layer was  
2 dried over anhydrous magnesium sulfate and concentrated under reduced  
3 pressure. Residual material was solidified from dichloromethane-ethyl ether-  
4 heptane to provide 397 mg of product (yield 82%), 1-benzenesulfonyl-5-  
5 methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-  
6 benzimidazole and 1-benzenesulfonyl-6-methoxy-2-[(3,5-dimethyl-4-methoxy-  
7 2-pyridyl)methylsulfinyl]-1H-benzimidazole.

10 EXAMPLES 2-19

11 The compounds listed under Examples 2-19 below were prepared using the  
12 method A as described in Example 1. 2-Pyridylmethylsulfinyl benzimidazole  
13 compounds were reacted with the corresponding arylsulfonyl chloride to give  
14 the corresponding 1-arylsulfonyl-2-pyridylmethylsulfinyl benzimidazoles as  
15 shown in Table 1 with reference to **Formula 21**.



27 Formula 21

1

2

TABLE 1

3	#	R <sub>6</sub> *	R <sub>1</sub> *	R <sub>2</sub> *	R <sub>3</sub> *	R <sub>17</sub> *	Yield (%)	m.p. (°C)
4	2	5-OCH <sub>3</sub> <sup>1</sup>	-CH <sub>3</sub>	-OCH <sub>3</sub>	-CH <sub>3</sub>	4-Cl	81	76-78
5	3	5-OCH <sub>3</sub> <sup>1</sup>	-CH <sub>3</sub>	-OCH <sub>3</sub>	-CH <sub>3</sub>	4-Br	73	84-86
6	4	5-OCH <sub>3</sub> <sup>1</sup>	-CH <sub>3</sub>	-OCH <sub>3</sub>	-CH <sub>3</sub>	4-F	85	70-72
7	5	5-OCH <sub>3</sub> <sup>1</sup>	-CH <sub>3</sub>	-OCH <sub>3</sub>	-CH <sub>3</sub>	4-CH <sub>3</sub>	79	64-66
8	6	5-OCH <sub>3</sub>	-CH <sub>3</sub>	-OCH <sub>3</sub>	-CH <sub>3</sub>	4-OCH <sub>3</sub>	83	85-87
9	7	5-OCH <sub>3</sub> <sup>1</sup>	-CH <sub>3</sub>	-OCH <sub>3</sub>	-CH <sub>3</sub>	3-CF <sub>3</sub>	67	65-67
10	8	5-OCH <sub>3</sub> <sup>1</sup>	-CH <sub>3</sub>	-OCH <sub>3</sub>	-CH <sub>3</sub>	4-OCF <sub>3</sub>	78	63-64
11	9	H	-CH <sub>3</sub>	OCH <sub>2</sub> CF <sub>3</sub>	H	H	78	80-83
12	10	H	-CH <sub>3</sub>	OCH <sub>2</sub> CF <sub>3</sub>	H	4-Cl	79	90-92
13	11	H	-CH <sub>3</sub>	OCH <sub>2</sub> CF <sub>3</sub>	H	4-Br	71	105-107
14	12	H	-CH <sub>3</sub>	OCH <sub>2</sub> CF <sub>3</sub>	H	4-F	73	85-87
15	13	H	-CH <sub>3</sub>	OCH <sub>2</sub> CF <sub>3</sub>	H	4-CH <sub>3</sub>	67	125-126
16	14	H	-CH <sub>3</sub>	OCH <sub>2</sub> CF <sub>3</sub>	H	4-OCH <sub>3</sub>	78	94-95
17	15	H	-CH <sub>3</sub>	OCH <sub>2</sub> CF <sub>3</sub>	H	3-CF <sub>3</sub>	67	123-125
18	16	H	-CH <sub>3</sub>	OCH <sub>2</sub> CF <sub>3</sub>	H	4-OCF <sub>3</sub>	78	125-126
19	17 <sup>2</sup>	5-OCHF <sub>2</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	H	H	92	51-54
20	18 <sup>2</sup>	5-OCHF <sub>2</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	H	4-OCH <sub>3</sub>	87	67-69
21	19 <sup>2</sup>	5-OCHF <sub>2</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	H	4-OCF <sub>3</sub>	87	61-63

22 <sup>1</sup> signifies a 3:2 ratio of 5-OCH<sub>3</sub> and 6-OCH<sub>3</sub>23 <sup>2</sup> signifies a 5:4 ratio of 5-OCHF<sub>2</sub> and 6-OCHF<sub>2</sub>

## 1 EXAMPLE 20

2 5-Difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-  
 3 benzimidazole, sodium salt sesquihydrate (432 mg, 1 mmole) was suspended in 30  
 4 ml of dichloromethane in the presence of anhydrous sodium carbonate (100 mg).  
 5 4-Chlorobenzenesulfonyl chloride (211 mg, 1 mmole) was added to the suspension  
 6 and stirred at 4 °C overnight. The organic layer was separated by filtration and  
 7 concentrated under reduced pressure. The residual solid was crystallized from  
 8 dichloromethane-ethyl ether-heptane. 417 mg of isomer, 1-(4-  
 9 chlorobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-  
 10 pyridyl)methylsulfinyl]-1H-benzimidazole and 1-(4-chlorobenzenesulfonyl)-6-  
 11 difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole  
 12 (5:4 ratio by NMR), was obtained. Yield 74.5% M.P. 82-83 °C.

13 <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ: 8.05-8.15(m, 2H), 8.0(d, 1H), 7.78-7.81(m, 1H), 7.45-7.6(m,  
 14 2H), 7.2-7.3(m, 1H), 6.80-6.81(d, 1H), 6.5-6.6(d, 1H), 4.9-5.0(q, 2H), 3.93(s, 3H).

15

## 16 EXAMPLES 21-24

17 The compounds listed in Table 2, with reference to **Formula 20**, were prepared  
 18 using the method described in Example 20.

19

20

TABLE 2

21	%	R <sub>6</sub> *	R <sub>1</sub> *	R <sub>2</sub> *	R <sub>3</sub> *	R <sub>17</sub> *	Yield(%)	m.p. (°C)
22	21 <sup>1</sup>	5-OCHF <sub>2</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	H	4-Br	87	80-82
23	22 <sup>1</sup>	5-OCHF <sub>2</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	H	4-F	78	67-70
24	23 <sup>1</sup>	5-OCHF <sub>2</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	H	4-CH <sub>3</sub>	88	73-75
25	24 <sup>1</sup>	5-OCHF <sub>2</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	H	3-CF <sub>3</sub>	83	62-66

26 <sup>1</sup> signifies a 5:4 ratio of 5-OCHF<sub>2</sub> and 6-OCHF<sub>2</sub>

## 1 EXAMPLE 25

2 1-(Pyridine-3-sulfonyl)-5-methoxy-2-[[3,5-dimethyl-4-methoxy-2-  
3 pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(pyridine-3-sulfonyl)-6-  
4 methoxy-2-[[3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-  
5 benzimidazole  
6 5-Methoxy-2-[[3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-  
7 benzimidazole (344 mg) was dissolved in 20 ml of dichloromethane and 1 ml of  
8 triethylamine. Pyridine-3-sulfonyl chloride (195 mg) was added and stirred in ice-  
9 bath for 3 hr. Dichloromethane layer was washed with an aqueous solution  
10 composed of 0.1 M NaCl and 0.1 M sodium bicarbonate. Dichloromethane layer  
11 was dried over anhydrous magnesium sulfate. Solvent was removed under reduced  
12 pressure. Residual material was precipitated by dichloromethane-ethyl ether-  
13 heptane to provide 372 mg of product, which were a mixture of 1-(pyridine-3-  
14 sulfonyl)-5-methoxy-2-[[3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-  
15 benzimidazole and 1-(pyridine-3-sulfonyl)-6-methoxy-2-[[3,5-dimethyl-4-  
16 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (3:1 ratio by NMR).  
17 M.P. 136-138 °C (decomposition)  
18 NMR (CDCl<sub>3</sub>, δ): 2.27 (s, 3H), 2.35 (s, 3H), 3.82 (s, 3H), 3.86 & 3.93 (2s, total  
19 3H), 5.04-5.17 (q, AB, 2H), 7.01-7.02 (dd, 1H), 7.47-7.56 (m, 2H), 7.67-7.71 (d,  
20 1H), 8.15 (s, 1H), 8.51-8.55 (dd, 1H), 8.85-8.88 (d, 1H), 9.34 (s, 1H)

21

## 22 EXAMPLE 26

23 1-(Pyridine-3-sulfonyl)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-  
24 pyridyl)methyl]sulfinyl]-1H-benzimidazole  
25 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl]sulfinyl]-1H-  
26 benzimidazole (370 mg) was dissolved in 20 ml of dichloromethane and 1 ml of  
27 triethylamine. Pyridine-3-sulfonyl chloride (195 mg) was added and stirred in ice-  
28 bath for 5 hr. Dichloromethane layer was washed with an aqueous solution



1 composed of 0.1 M NaCl and 0.1 M sodium bicarbonate. Dichloromethane layer  
2 was dried over anhydrous magnesium sulfate. Solvent was removed under reduced  
3 pressure. Residual material was precipitated by dichloromethane-ethyl ether-  
4 heptane to provide 348 mg of 1-(pyridine-3-sulfonyl)-2-[(3-methyl-4-(2,2,2-  
5 trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole.

6 M.P. 118-120 °C (decomposition)

7 NMR (CDCl<sub>3</sub>, δ): 2.35 (s, 3H), 4.38-4.49 (q, 2H), 4.98-5.22 (q, AB, 2H), 6.73 (d,  
8 1H), 7.41-7.56 (m, 3H), 7.80-8.02 (dd, 2H), 8.23 (s, 1H), 8.52 (dd, 1H), 8.87 (dd,  
9 1H), 9.36 (s, 1H)

10

#### 11 EXAMPLE 27

12 1-(Pyridine-3-sulfonyl)-5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-  
13 pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(pyridine-3-sulfonyl)-6-  
14 (difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-  
15 benzimidazole

16 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-  
17 benzimidazole (383 mg) was dissolved in 20 ml of dichloromethane and 1 ml of  
18 triethylamine. Pyridine-3-sulfonyl chloride (195 mg) was added and stirred in ice-  
19 bath for 5 hr. Dichloromethane layer was washed with an aqueous solution  
20 composed of 0.1 M NaCl and 0.1 M sodium bicarbonate. Dichloromethane layer  
21 was dried over anhydrous magnesium sulfate. Solvent was removed under reduced  
22 pressure. Residual material was precipitated by dichloromethane-ethyl ether-  
23 heptane to provide 397 mg of a mixture of 1-(pyridine-3-sulfonyl)-5-  
24 (difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-  
25 benzimidazole and 1-(pyridine-3-sulfonyl)-6-(difluoromethoxy)-2-[(3,4-  
26 dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (ratio 3:2 by NMR).

27 M.P. 127-128 °C (decomposition)

28

## 1 EXAMPLE 28

2 Preparation of 1-(morpholin-4-yl)phenylsulfonyl-5-methoxy-2-[(3,5-dimethyl-4-  
3 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(morpholin-4-  
4 yl)phenylsulfonyl-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
5 pyridyl)methyl]sulfinyl]-1H-benzimidazole

6 270.8 mg of 4-(p-chlorosulfonyl)phenyl morpholine was added to 344 mg of 5-  
7 Methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-  
8 benzimidazole in 20 ml of dichloromethane and 0.5 ml of triethylamine. The  
9 reaction mixture was stirred at room temperature overnight. Dichloromethane layer  
10 was washed with water, and dried over anhydrous magnesium sulfate. Organic  
11 layer was evaporated. Residual material was lyophilized in vacuo to give 425 mg  
12 of the titled product (1:1 ratio by NMR).

13 m.p.; 76-79 °C (decomposition)

14

## 15 EXAMPLE 29

16 Preparation of N-[4-[[5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
17 pyridyl)methyl]sulfinyl]benzimidazol-1-yl]sulfonyl]phenyl]urea and N-[4-[[6-  
18 methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]benzimidazol-1-  
19 yl]sulfonyl]phenyl]urea

20 128 mg of N-[4-(chlorosulfonyl)phenyl]urea was added to 172 mg of 5-Methoxy-  
21 2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole in a  
22 mixture of 0.5 ml of triethylamine and 10 ml of dichloromethane-acetonitrile  
23 (50/50). The reaction mixture was stirred at room temperature overnight.  
24 Dichloromethane (20 ml) was added and washed with water, and 0.1 M sodium  
25 bicarbonate solution. Organic layer was dried over anhydrous magnesium sulfate  
26 and evaporated. Residue was dissolved in 2 ml of dichloromethane and ethyl ether  
27 was added for crystallization. Crystals were collected and dried. 190 mg of product  
28 was obtained. The product was composed of a mixture of N-[4-[[5-methoxy-2-

1 [[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]benzimidazol-1-  
2 yl)sulfonyl]phenyl]urea and N-[4-[[6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
3 pyridyl)methyl]sulfinyl]benzimidazol-1-yl)sulfonyl]phenyl]urea (4:3 ratio by  
4 NMR).

5 m.p.; 154-158 °C (decomposition)

6 NMR (CDCl<sub>3</sub>, δ): 2.19 (s, 3H), 2.20 & 2.21 (2s, total 3H), 3.69 & 3.70 (2s, total  
7 3H), 3.76 & 3.89 (2s, total 3H), 4.75-4.94 (q, AB, 2H), 5.6-5.7 (br, NH<sub>2</sub>), 6.95-  
8 7.08 (d, 1H), 7.05 (s, 1H), 7.43-7.86 (m, 5H), 8.12 (s, 1H), 9.0 (br, NH)

9

#### 10 EXAMPLE 30

11 Preparation of N-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-  
12 pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenyl)urea

13 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-  
14 benzimidazole (185 mg) dissolved in 30 ml of dichloromethane and 0.4 ml of  
15 triethylamine was added to 128 mg of N-[4-(chlorosulfonyl)phenyl]urea. The  
16 reaction mixture was stirred at room temperature overnight. The reaction mixture  
17 was washed with water and 0.1 N sodium bicarbonate solution. Organic layer was  
18 dried over anhydrous magnesium sulfate, and concentrated under reduced  
19 pressure. Residue was dissolved in 2 ml of dichloromethane and ethyl ether was  
20 added for precipitation. 125 mg of the titled product was obtained.

21 M.P. 115 °C (decomposition)

22 NMR (CDCl<sub>3</sub>, δ): 2.25 (s, 3H), 4.37-4.42 (q, 2H), 4.6-4.85 (q, AB, 2H), 6.67 (d,  
23 1H), 7.35-7.42 (m, 2H), 7.61-7.75 (m, 3H), 7.89-8.05 (m, 2H), 8.27-8.38 (m, 2H)

24

#### 25 EXAMPLE 31

26 Preparation of 15-[(5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-  
27 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]-

28 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene and 15-[(6-

1 methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl}benzimidazol-1-  
2 yl)sulfonyl]- 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene  
3 170 mg of 5-methoxy-2-[[3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-  
4 1H-benzimidazole  
5 and 190 mg of m-(chlorosulfonyl) benzo-15-crown-5-ether were dissolved in 0.2  
6 ml of triethylamine and 20 ml of dichloromethane. The reaction mixture was  
7 stirred at room temperature overnight. Organic layer was washed with water and  
8 dried over anhydrous magnesium sulfate. Solvent was removed to give syrup,  
9 which was lyophilized. 210 mg of the titled product, a mixture of 15-[(5-methoxy-  
10 2-{[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl}benzimidazol-1-  
11 yl)sulfonyl]- 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene and  
12 15-[(6-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-  
13 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]-  
14 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene (1:1 ratio by  
15 NMR), was obtained. Lyophilized product showed M.P. 76-80 °C with  
16 decomposition.  
17 NMR (CDCl<sub>3</sub>, δ): 2.21 (s, 3H), 2.31 (s, 3H), 3.68-3.73 (m, 8H), 3.74 (s, 3H), 3.84-  
18 3.87 (m, 4H), 3.90 (s, 3H), 4.10-4.13 (m, 4H), 4.81-4.95 (2q, 2AB, 2H), 6.84 (d,  
19 1H), 7.00-7.07 (dd, 1H), 7.25 (d, 1H), 7.42-7.72 (m, 3H), 8.15 (s, 1H)  
20

#### 21 EXAMPLE 32

22 Preparation of 15-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-  
23 pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}-  
24 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene  
25 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl]sulfinyl]-1H-  
26 benzimidazole (185 mg) dissolved in 20 ml of dichloromethane and 0.2 ml of  
27 triethylamine was added to 190 mg of m-(chlorosulfonyl) benzo-15-crown-5-ether.  
28 The reaction mixture was stirred at room temperature overnight. Organic layer was

1 washed with water and dried over anhydrous magnesium sulfate. Solvent was  
2 removed to give syrup, which was lyophilized. 231 mg of the titled product was  
3 obtained. Lyophilized product showed M.P. 76-80 °C with decomposition.  
4 NMR (CDCl<sub>3</sub>, δ): 2.33 (s, 3H), 3.66-3.73 (m, 8H), 3.83-3.87 (m, 4H), 4.10-4.12  
5 (m, 4H), 4.35-4.41 (q, 2H), 4.84-5.05 (q, AB, 2H), 6.61 (d, 1H), 6.86 (d, 1H),  
6 7.37-7.45 (m, 2H), 7.56 (s, 1H), 7.71-7.74 (dd, 2H), 7.95 (d, 1H), 8.23 (d, 1H)

7

## 8 EXAMPLE 33

9 Preparation of 2-{4-[(5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
10 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-  
11 pyridyl)acetamide and 2-{4-[(6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
12 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-  
13 pyridyl)acetamide

14 170 mg of 2-[p-(chlorosulfonyl)phenoxy]-N-(2-pyridyl)acetamide was added to  
15 172 mg of 5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-  
16 1H-benzimidazole dissolved in dichloromethane (15 ml) and triethylamine (0.4  
17 ml). The reaction mixture was stirred at room temperature overnight. The reaction  
18 mixture was washed with water. Organic layer was dried over anhydrous  
19 magnesium sulfate, and evaporated. Residual material was lyophilized in vacuo to  
20 give 244 mg of the titled product, which was a mixture of 2-{4-[(5-methoxy-2-  
21 {[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-  
22 yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide and 2-{4-[(6-methoxy-2-[(3,5-  
23 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-  
24 yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide (2:1 ratio by NMR).  
25 M.P. 76-80 °C  
26 NMR (CDCl<sub>3</sub>, δ): 2.21 & 2.23 (2s, total 3H), 2.32 (s, 3H), 3.74 & 3.75 (2s, total  
27 3H), 3.83 & 3.93 (2s, total 3H), 4.65 (s, 2H), 4.83-4.92 (q, AB, 2H), 6.99-7.11 (m,  
28 5H), 7.46 (d, 1H), 7.68-7.88 (m, 2H), 8.75 (br, NH)

## 1 EXAMPLE 34

2 Preparation of 2-(4-{[2-([3-methyl-4-(2,2,2-trifluoroethoxy)-2-3 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl}phenoxy)-N-(2-4 pyridyl)acetamide

5 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl]sulfinyl]-1H-

6 benzimidazole (185 mg) dissolved in 20 ml of dichloromethane and 0.2 ml of

7 triethylamine was added to 170 mg of 2-[p-(chlorosulfonyl)phenoxy]-N-(2-

8 pyridyl)acetamide. The reaction mixture was washed with water. Organic layer

9 was dried over anhydrous magnesium sulfate, and evaporated. Residual material

10 was lyophilized to give 237 mg of the titled product. M.P. 78-81 °C.

11 NMR (CDCl<sub>3</sub>, δ): 2.31 (s, 3H), 4.34-4.40 (q, 2H), 4.71 (s, 2H), 4.84-5.05 (q, AB,

12 2H), 6.62 (d, 1H), 7.09 (d, 2H), 7.29-7.47 (m, 2H), 7.62-7.80 (m, 2H), 7.98 (d,

13 1H), 8.11 (d, 2H), 8.20-8.29 (m, 4H), 8.92 (br, NH)

14

## 15 EXAMPLE 35

16 Preparation of 2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-17 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-18 pyridyl)acetamide and 2-{4-[(6-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-19 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-20 pyridyl)acetamide

21 5-(difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-

22 benzimidazole (192 mg) dissolved in 20 ml of dichloromethane and 0.2 ml of

23 triethylamine was added to 170 mg of 2-[(p-

24 chlorosulfonyl)phenoxyacetyl]aminopyridine. The reaction mixture was washed

25 with water. Organic layer was dried over anhydrous magnesium sulfate, and

26 evaporated. Residual material was lyophilized to give 187 mg of the titled product,

27 which was a mixture of 2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-

28 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-

1 pyridyl)acetamide and 2-{4-[(6-(difluoromethoxy)-2-[(3,4-dimethoxy-2-  
2 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-  
3 pyridyl)acetamide (2:1 ratio by NMR).  
4 M.P. 95-101 °C  
5 NMR (CDCl<sub>3</sub>, δ): 3.90 (s, 3H), 3.93 (s, 3H), 4.67 (s, 2H), 4.85-5.00 (2q, 2AB, 2H;  
6 s like, 1H), 6.52-6.80 (m, 2H), 7.08 (m, 3H), 7.29-7.40 (d, 1H), 7.58-7.80 (m, 2H),  
7 7.97-8.16 (m, 3H), 8.22 (d, 1H), 8.30 (d, 1H), 8.82 (br, NH)

8

## 9 EXAMPLE 36

10 Preparation of 1-[4-(3-(morpholin-4-yl) propoxy) benzenesulfonyl]-5-  
11 (difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-  
12 benzimidazole and 1-[4-(3-(morpholin-4-yl) propoxy) benzenesulfonyl]-6-  
13 (difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-  
14 benzimidazole

15 180 mg of 4-(3-(morpholin-4-yl) propoxy) benzenesulfonyl chloride was added to  
16 a solution of 190 mg of 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-  
17 pyridyl)methyl]sulfinyl]-1H-benzimidazole in 10 ml of dichloromethane and 0.5  
18 ml of triethylamine. The reaction mixture was stirred overnight, and washed with  
19 water. Organic layer was concentrated and lyophilized in vacuo. 210 mg of the  
20 titled mixture was obtained (1:1 ratio by NMR).

21

## 22 EXAMPLE 37

23 Preparation of 1-[4-[3-(morpholin-4-yl) propoxy] benzenesulfonyl]-5-methoxy-2-  
24 [(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-[  
25 4-[3-(morpholin-4-yl) propoxy] benzenesulfonyl]-6-methoxy-2-[(3,5-dimethyl-4-  
26 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

27 200 mg of 4-[3-(morpholin-4-yl) propoxy] benzenesulfonyl chloride was added to  
28 a solution of 200 mg of 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-

1 pyridyl)methyl]sulfinyl]-1H-benzimidazole in 10 ml of dichloromethane and 0.5  
2 ml of triethylamine. The reaction mixture was stirred overnight, and washed with  
3 water. Organic layer was concentrated and treated with ethyl ether to give solids.  
4 Solids were crystallized from dichloromethane and ether. 210 mg of the titled  
5 product, 1:1 ratio of 5-methoxy and 6-methoxy compound, was obtained.  
6 M.P. 98-102 °C (decomposition)  
7 NMR (CDCl<sub>3</sub>, δ): 1.97-2.05 (m, 2H), 2.09 (s, 3H), 2.20 (s, 3H) 3.05-3.15 (m, 6H),  
8 3.58 (s, 3H), 3.65-3.80 (m, 4H), 3.81 & 3.92 (2s, total 3H), 3.82-3.95 (t, 2H), 4.73-  
9 4.94 (q, AB, 2H), 6.89-6.91 (d, 2H), 7.4-7.6 (m, 3H), 7.79-8.0 (m, 2H), 8.17 (s,  
10 1H)

11

## 12 EXAMPLE 38

13 Preparation of 1-[(N,N-dimethylamino)methyl]benzene-4-sulfonyl]-5-methoxy-2-  
14 [(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-  
15 [(N,N-dimethylamino)methyl]benzene-4-sulfonyl]-6-methoxy-2-[(3,5-dimethyl-  
16 4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

17 120 mg of N-[p-(chlorosulfonyl)phenyl]methyl]-N,N-dimethylamine was added  
18 to 172 mg of 5-Methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-  
19 1H-benzimidazole dissolved in 20 ml of dichloromethane and 0.5 ml of  
20 triethylamine. The reaction mixture was stirred at room temperature for 16 hr.  
21 Dichloromethane layer was washed with water, and 0.1 N sodium bicarbonate  
22 solution. The organic layer was dried over anhydrous magnesium sulfate and  
23 concentrated under reduced pressure. Residual material was lyophilized in vacuo  
24 to give 245 mg of the titled product (1:1 ratio by NMR).

25

## 26 EXAMPLE 39

27 Preparation of 1-[2-acetamido-4-methyl-5-thiazolylsulfonyl]-5-methoxy-2-[(3,5-  
28 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole



1 172 mg of 5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-  
2 1H-benzimidazole was dissolved in 10 ml of dichloromethane and 0.4 ml of  
3 triethylamine, and 128 mg of 2-acetamido-4-methyl-5-thiazolyl sulfonyl chloride  
4 was added. The reaction mixture was stirred at room temperature for 15 hr.  
5 Product spot was shown at slightly higher position than 5-methoxy-2-[[[(3,5-  
6 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole in thin layer  
7 chromatography (developing solvent: dichloromethane-acetonitrile-methanol =  
8 100:10:5). Product was separated by silica gel column chromatography. 145 mg of  
9 the titled product was isolated.

10

## 11 EXAMPLE 40

12 Preparation of 1-(thiophene-2-sulfonyl)-5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-  
13 2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(thiophene-2-sulfonyl)-6-  
14 methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-  
15 benzimidazole

16 172 mg of 5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-  
17 1H-benzimidazole was dissolved in 10 ml of dichloromethane and 0.2 ml of  
18 triethylamine. 95 mg of thiophene-2-sulfonyl chloride was added. . The reaction  
19 mixture was stirred at room temperature for 16 hr. Dichloromethane layer was  
20 washed with water and concentrated under reduced pressure. Residual material  
21 was crystallized from acetonitrile-ethyl ether-hexane. 225 mg of the titled product,  
22 a mixture of 1-(thiophene-2-sulfonyl)-5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-  
23 pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(thiophene-2-sulfonyl)-6-  
24 methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-  
25 benzimidazole (7:1 ratio by NMR), was obtained.

26 M.P. 86-90 °C

27 NMR (CDCl<sub>3</sub>, δ): 2.20 (s, 3H), 2.30 (s, 3H), 3.73 (s, 3H), 3.83 & 3.91 (2s, total  
28 3H), 4.80-4.92 (q, AB, 2H), 7.00-7.10 (m, 2H), 7.47 (s, 1H), 7.67-7.69 (m, 2H),

1 7.97-7.99 (d, 1H), 8.13 (s, 1H)

2

3 EXAMPLE 41

4 Preparation of 1-(phenylmethylsulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-  
5 2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(phenylmethylsulfonyl)-6-  
6 methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-  
7 benzimidazole

8 172 mg of 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-  
9 1H-benzimidazole was dissolved in 10 ml of dichloromethane and 0.2 ml of  
10 triethylamine. 95 mg of phenylmethylsulfonyl chloride was added. . The reaction  
11 mixture was stirred at room temperature for 36 hr. Dichloromethane layer was  
12 washed with water and concentrated under reduced pressure. Residual material  
13 was lyophilized in vacuo to give 205 mg of the titled product, a mixture of 1-  
14 (phenylmethylsulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
15 pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(phenylmethylsulfonyl)-6-  
16 methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-  
17 benzimidazole (2:1 ratio by NMR)  
18 M.P. 130 °C (decomposition)

19

20 EXAMPLE 42

21 Preparation of 1-(n-propanesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
22 pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(n-propanesulfonyl)-6-methoxy-  
23 2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

24 103 mg of 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-  
25 1H-benzimidazole was dissolved in 2 ml of chloroform and 0.1 ml of  
26 triethylamine. 1-Propanesulfonyl chloride (0.042 ml) was slowly added in ice bath.  
27 The reaction mixture was stirred at room temperature for 3 hr. Organic layer was  
28 washed with cold 0.1 N sodium bicarbonate solution. Chloroform layer was dried

1 over anhydrous magnesium sulfate, and concentrated under reduced pressure.  
2 Residual material was solidified from chloroform-ethyl ether-hexane to give 128  
3 mg (95%) of the titled product (3:2 ratio).  
4 M.P. 96-100 °C

5

## 6 EXAMPLE 43

7 Preparation of 1-(n-butanesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
8 pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(n-butanesulfonyl)-6-methoxy-  
9 2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

10 103 mg of 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-  
11 1H-benzimidazole was dissolved in 2 ml of chloroform and 0.1 ml of  
12 triethylamine. 1-Butanesulfonyl chloride (0.042 ml) was slowly added in ice bath.  
13 The reaction mixture was stirred at room temperature for 3 hr. Organic layer was  
14 washed with cold 0.1 N sodium bicarbonate solution. Chloroform layer was dried  
15 over anhydrous magnesium sulfate, and concentrated under reduced pressure.  
16 Residual material was solidified from chloroform-ethyl ether-hexane to give 130  
17 mg (93%) of the titled product (3:2 ratio).  
18 M.P. 54-56 °C

19

## 20 EXAMPLE 44

21 Preparation of 1-(isopropylsulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
22 pyridyl)methyl]sulfinyl]-1H-benzimidazole and -(isopropylsulfonyl)-6-methoxy-2-  
23 [(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

24 103 mg of 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-  
25 1H-benzimidazole was dissolved in 2 ml of chloroform and 0.1 ml of  
26 triethylamine. Isopropylsulfonyl chloride (0.042 ml) was slowly added in ice bath.  
27 The reaction mixture was stirred at room temperature for 24 hr. Organic layer was  
28 concentrated under reduced pressure and applied to silica gel column

1 chromatography. 78 mg of the titled product was isolated (1:1 ratio).

2 M.P. 105-108 °C (decomposition)

3

4 EXAMPLE 45

5 1-[(N,N-dimethylamino)benzene-4-sulfonyl]-5-methoxy-2-[(3,5-dimethyl-4-  
6 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-[(N,N-  
7 dimethylamino)benzene-4-sulfonyl]-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
8 pyridyl)methyl]sulfinyl]-1H-benzimidazole

9 120 mg of p-(N,N-dimethylamino)benzenesulfonyl chloride was added to 172 mg  
10 of 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-  
11 benzimidazole dissolved in 20 ml of dichloromethane and 0.5 ml of triethylamine.  
12 The reaction mixture was stirred at room temperature for 16 hr. Dichloromethane  
13 layer was washed with water and 0.1 N sodium carbonate solution. Organic layer  
14 was dried over anhydrous magnesium sulfate and was concentrated under reduced  
15 pressure. Residual material was lyophilized in vacuo to give 215 mg of the titled  
16 product (1:1 ratio).

17 M.P. 92-96 °C

18 NMR (CDCl<sub>3</sub>, δ): 2.24 (s, 3H), 2.30 (s, 3H), 3.02 (s, 3H), 3.03 (s, 3H), 3.75 (s,  
19 3H), 3.83 & 3.92 (2s, total 3H), 4.77-4.94 (2q, AB & A'B', total 2H), 6.57-6.61  
20 (m, 2H), 6.96-7.07 (m, 1H), 7.48 & 7.68 (2d, total 1H), 7.85-7.90 (m, 3H), 8.22 (s,  
21 1H)

22

23 EXAMPLE 46

24 Preparation of N-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-2-  
25 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl} phenyl)urea

26 128 mg of N-[4-(chlorosulfonyl)phenyl]urea was added to 191 mg of 2-[(3-  
27 methyl-4-methoxypropoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole sodium  
28 salt in a mixture of 0.1 ml of triethylamine and 10 ml of dichloromethane-

1 acetonitrile (50/50). The reaction mixture was stirred at room temperature  
2 overnight. Dichloromethane (20 ml) was added and washed with water, and 0.1 M  
3 sodium bicarbonate solution. Organic layer was dried over anhydrous magnesium  
4 sulfate and evaporated. Residue was dissolved in minimum amounts of acetonitrile  
5 and ethyl ether was added for crystallization. Crystals were collected and dried.  
6 190 mg of the titled product was obtained.  
7 NMR (CDCl<sub>3</sub>, δ): 2.03-2.07 (m, 2H), 2.18 (s, 3H), 3.34 (s, 3H), 3.52-3.54 (t, 2H),  
8 4.05-4.08 (t, 2H), 4.76-5.00 (q, AB, 2H), 5.50-5.61 (br, -NH<sub>2</sub>), 6.69 (d, 1H), 7.33-  
9 7.37 (m, 3H), 7.51 (d, 1H), 7.65 (d, 1H), 7.81 (d, 2H), 7.98 (d, 1H), 8.17 (d, 1H),  
10 8.97 (s, -NH-)

11

## 12 EXAMPLE 47

13 Preparation of 1-(pyridine-3-sulfonyl)-2-[[[3-methyl-4-(3-methoxypropoxy)-2-  
14 pyridyl]methyl]sulfinyl]-1H-benzimidazole

15 100 mg of pyridine-3-sulfonyl chloride was added to 191 mg of 2-[[[3-methyl-4-  
16 (3-methoxypropoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole sodium salt in  
17 a mixture of 0.15 ml of triethylamine and 10 ml of dichloromethane. The reaction  
18 mixture was stirred at room temperature overnight. Dichloromethane (20 ml) was  
19 added and washed with water, and 0.1 M sodium bicarbonate solution. Organic  
20 layer was dried over anhydrous magnesium sulfate and evaporated. Residue was  
21 dissolved in minimum amounts of acetonitrile and ethyl ether was added for  
22 precipitation. Solids was collected and dried to give 127 mg of the titled product.  
23 NMR (CDCl<sub>3</sub>, δ): 1.97-2.10 (m, 2H), 2.21 (s, 3H), 3.35 (s, 3H), 3.51-3.57 (t, 2H),  
24 4.04-4.07 (t, 2H), 4.82-5.14 (q, AB, 2H), 6.73 (d, 1H), 7.41-7.56 (m, 3H), 7.80-  
25 8.02 (dd, 2H), 8.23-8.87 (m, 3H), 9.34 (s, 1H)

26

## 27 EXAMPLE 48

28 Preparation of 2-(4-{[2-([4-(3-methoxypropoxy)-3-methyl-2-

1 pyridyl)methyl}sulfinyl)benzimidazol-1-yl)sulfonyl}phenoxy)-N-(2-  
2 pyridyl)acetamide  
3 170 mg of 2-[p-(chlorosulfonyl)phenoxy]-N-(2-pyridyl)acetamide was added to  
4 191 mg of 2-[[[4-(3-methoxypropoxy)-3-methyl-2- pyridyl)methyl}sulfinyl]-1H-  
5 benzimidazole sodium salt in dichloromethane (15 ml) and triethylamine (0.1 ml).  
6 The reaction mixture was stirred at room temperature overnight. The reaction  
7 mixture was washed with water. Organic layer was dried over anhydrous  
8 magnesium sulfate, and evaporated. Residual material was lyophilized in vacuo to  
9 give 244 mg of the titled product.

10 M.P. 78-81 °C (decomposition)

11 NMR (CDCl<sub>3</sub>, δ): 2.00-2.10 (m, 2H), 2.27 (s, 3H), 3.35 (s, 3H), 3.52-3.57 (t, 2H),  
12 4.06-4.10 (t, 2H), 4.64 (s, 2H), 4.83-5.02 (q, AB, 2H), 6.67 (d, 1H), 7.07-7.10 (m,  
13 3H), 7.32-7.49 (m, 3H), 7.70-7.82 (m, 2H), 7.99 (d, 1H), 8.14-8.30 (m, 4H), 8.77  
14 (br, NH)

15

#### 16 EXAMPLE 49

17 Preparation of 1-[4-(morpholin-4-yl)phenylsulfonyl]-2-[[[4-(3-methoxypropoxy)-  
18 3-methyl-2-pyridyl)methyl}sulfinyl]-1H-benzimidazole

19 136 mg of 4-[(p-chlorosulfonyl)phenyl] morpholine was added to 191 mg of 2-  
20 [[4-(3-methoxypropoxy)-3-methyl -2-pyridyl)methyl}sulfinyl]-1H-benzimidazole  
21 sodium salt in dichloromethane (15 ml) and triethylamine (0.1 ml). The reaction  
22 mixture was stirred at room temperature overnight. The reaction mixture was  
23 washed with water. Organic layer was dried over anhydrous magnesium sulfate,  
24 and evaporated. Residual material was lyophilized in vacuo to give 224 mg of the  
25 titled product.

26 M.P. 93-96 °C (decomposition)

27 NMR (CDCl<sub>3</sub>, δ): 2.02-2.06 (m, 2H), 2.26 (s, 3H), 3.2-3.3 (m, 4H), 3.35 (s, 3H),  
28 3.50-3.53 (t, 2H), 3.75-3.80 (m, 4H), 4.04-4.08 (t, 2H), 4.71-4.79 (q, AB, 2H),

1 6.71 (d, 1H), 7.26-7.5 (m, 4H), 7.8-8.1 (m, 2H), 8.27 (d, 1H)

2

3 EXAMPLE 50

4 Preparation of 1-[[2-(morpholin-4-yl)ethoxy]phenyl-4-sulfonyl]-2-[[[4-(3-  
5 methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole

6 136 mg of 4-[2-[(p-chlorosulfonyl)phenoxy]ethyl]morpholine was added to 191

7 mg of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-

8 benzimidazole sodium salt in dichloromethane (15 ml) and triethylamine (0.1 ml).

9 The reaction mixture was stirred at room temperature overnight. The reaction

10 mixture was washed with water. Organic layer was dried over anhydrous

11 magnesium sulfate, and evaporated. Residual material was lyophilized in vacuo to

12 give 234 mg of the titled product.

13 NMR (CDCl<sub>3</sub>, δ): 2.05-2.10 (m, 2H), 2.27 (s, 3H), 2.56 (m, 4H), 2.79-2.82 (t, 2H),

14 3.35 (s, 3H), 3.53-3.56 (t, 2H), 3.69-3.72 (m, 4H), 4.07-4.10 (t, 2H), 4.12-4.15 (t,

15 2H), 4.81-4.99 (q, AB, 2H), 6.68 (d, 1H), 6.95 (d, 2H), 7.36-7.46 (m, 2H), 7.81 (d,

16 1H), 7.99 (d, 1H), 8.06 (d, 2H), 8.21 (d, 1H)

17

18 EXAMPLE 51

19 Preparation of 1-(thiophene-2-sulfonyl)-2-[[[4-(3-methoxypropoxy)-3-methyl-2-  
20 pyridyl]methyl]sulfinyl]-1H-benzimidazole

21 92 mg of thiophene-2-sulfonyl chloride was added to 191 mg of 2-[[[4-(3-

22 methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole sodium

23 salt in dichloromethane (15 ml) and triethylamine (0.1 ml). The reaction mixture

24 was stirred at room temperature overnight. The reaction mixture was washed with

25 water. Organic layer was dried over anhydrous magnesium sulfate, and

26 evaporated. Residual material was lyophilized in vacuo to give 215 mg of the titled

27 product.

28 M.P. 147-150 °C

1 NMR (CDCl<sub>3</sub>, δ): 2.00-2.08 (m, 2H), 2.27 (s, 3H), 3.35 (s, 3H), 3.53-3.56 (s, 3H),  
2 4.07-4.10 (t, 2H), 4.83-5.00 (q, AB, 2H), 6.67 (d, 1H), 7.08-7.10 (t, 1H), 7.42-7.49  
3 (m, 2H), 7.68-7.70 (d, 1H), 7.82-7.84 (d, 1H), 8.00-8.03 (m, 2H), 8.18 (d, 1H)

4

#### 5 EXAMPLE 52

##### 6 Preparation of 1-benzenesulfonyl-2-[[[4-(3-methoxypropoxy)-3-methyl-2- 7 pyridyl]methyl]sulfinyl]-1H-benzimidazole

8 94 mg of benzenesulfonyl chloride was added to 191 mg of 2-[[[4-(3-  
9 methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole sodium  
10 salt in dichloromethane (15 ml) and triethylamine (0.1 ml). The reaction mixture  
11 was stirred at room temperature overnight. The reaction mixture was washed with  
12 water. Organic layer was dried over anhydrous magnesium sulfate, and  
13 evaporated. Residual material was crystallized from acetonitrile-ethyl ether. 210  
14 mg of the titled product was obtained.

15 M.P. 126-128 °C

16 NMR (CDCl<sub>3</sub>, δ): 1.97-2.09 (m, 2H), 2.27 (s, 3H), 3.34 (s, 3H), 3.52-3.57 (t, 3H),  
17 4.05-4.10 (t, 3H), 4.81-5.03 (q, AB, 2H), 6.66 (d, 1H), 7.38-7.53 (m, 4H), 7.61-  
18 7.65 (t, 1H), 7.80 (d, 1H), 8.00 (d, 1H), 8.11-8.16 (m, 3H)

19

#### 20 EXAMPLE 53

##### 21 Preparation of 2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2- 22 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide and 2-{4- 23 [(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-

##### 24 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide

25 5-Methoxy-2-[[[4-(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-  
26 benzimidazole (344 mg) was dissolved in 40 ml of dichloromethane and 1 ml of  
27 triethylamine. 2-[p-(chlorosulfonyl)phenoxy]acetamide (250 mg) was added. The  
28 reaction mixture was stirred at room temperature overnight. The reaction was



1 monitored by thin layer chromatography (developing solvent: chloroform-  
2 acetonitrile-methanol (100:10:7)). Solid was collected by filtration, washed with  
3 small amounts of dichloromethane, and dried in vacuo to give 415 mg of the titled  
4 product (3:2 ratio of 5-methoxy / 6-methoxy compound).

5 M.P. 159-161 °C (decomposition)

6 NMR (DMSO-d<sub>6</sub>, δ): 2.13 (s, 3H), 2.25 (s, 3H), 3.69 (s, 3H), 3.78 & 3.88 (2s,  
7 total 3H), 4.56 (s, 2H), 4.82-5.04 (2q, AB, 2H), 7.05-7.18 (m, 3H), 7.34-7.40 (m,  
8 1H), 7.60-7.90 (m, 2H), 8.12-8.18 (m, 2H)

9  
10 EXAMPLE 54

11 Preparation of 2-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-  
12 pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)acetamide  
13 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-  
14 benzimidazole (370 mg) was dissolved in 20 ml of dichloromethane and 1 ml of  
15 triethylamine. 2-[p-(chlorosulfonyl)phenoxy]acetamide(250 mg) was added. The  
16 reaction mixture was stirred at room temperature for 24 hr. Solid was collected,  
17 washed with dichloromethane, and dried in vacuo. 378 mg of the titled product  
18 was obtained.

19 M.P. 162-166 °C (decomposition)

20 NMR (DMSO-d<sub>6</sub>, δ): 2.21 (s, 3H), 4.55 (s, 2H), 4.86-5.15 (q, 2H and q, 2H) 6.99  
21 (d, 1H), 7.16 (d, 2H), 7.39-7.58 (m, 2H), 7.79 (d, 1H), 7.97-8.03 (m, 2H), 8.17 (d,  
22 2H)

23  
24 EXAMPLE 55

25 Preparation of 2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-  
26 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide and 2-{4-  
27 [(6-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-  
28 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide

1 5-(difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-  
2 benzimidazole (383 mg) was dissolved in 20 ml of dichloromethane and 1 ml of  
3 triethylamine. 2-[p-(chlorosulfonyl)phenoxy]acetamide(250 mg) was added. The  
4 reaction mixture was stirred at room temperature for 24 hr. Solid was collected,  
5 washed with dichloromethane, and dried in vacuo. 413 mg of the titled product  
6 (1:1 ratio) was obtained.

7 M.P. 125-128 °C (decomposition)

8

#### 9 EXAMPLE 56

10 Preparation of 2-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-2-  
11 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl} phenoxy)acetamide  
12 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-  
13 benzimidazole sodium salt (382 mg) was added in dichloromethane (45 ml) and  
14 triethylamine (0.1 ml). 2-[p-(chlorosulfonyl)phenoxy]acetamide(250 mg) was  
15 added. The reaction mixture was stirred at room temperature overnight. The  
16 reaction mixture was washed with water. Organic layer was dried over anhydrous  
17 magnesium sulfate, and evaporated. Residual material was crystallized from  
18 acetonitrile-ethyl ether. 437 mg of the titled product was obtained.

19 M.P. 148-153 °C (decomposition)

20 NMR (DMSO-d<sub>6</sub>, δ): 1.93-1.97 (m, 2H), 2.18 (s, 3H), 3.35 (s, 3H), 3.46 (t, 2H),  
21 4.06 (t, 2H), 4.56 (s, 2H), 4.83-5.13 (q, AB, 2H), 6.85 (d, 1H), 7.16 (d, 2H), 7.41-  
22 7.60 (m, 2H), 7.79 (d, 1H), 7.89 (d, 1H), 8.00-8.02 (d, 1H), 8.16-8.18 (d, 2H)

23

#### 24 EXAMPLE 57

25 Preparation of 1-[{2-(morpholin-4-yl)ethoxy} phenyl-4-sulfonyl]-2-[(3-methyl-4-  
26 (2,2,2-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole  
27 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-  
28 benzimidazole (370 mg) was dissolved in 20 ml of dichloromethane and 1 ml of

1 triethylamine. [2-(Morpholin-4-yl)ethoxy]phenyl-4-sulfonyl chloride (273 mg)  
2 was added and stirred at room temperature overnight. Dichloromethane layer was  
3 washed with an aqueous solution composed of 0.1 M NaCl and ice-cooled 0.1 N  
4 sodium bicarbonate solution. Dichloromethane layer was dried over anhydrous  
5 magnesium sulfate. Solvent was removed under reduced pressure. Residual  
6 material was lyophilized to provide 515 mg of the titled product.  
7 NMR (CDCl<sub>3</sub>, δ): 2.33 (s, 3H), 2.50-2.52 (m, 4H), 2.78-2.81 (t, 2H), 3.70-3.74 (m,  
8 4H), 4.12-4.15 (t, 2H), 4.84-5.02 (q, AB, 2H), 6.63 (d, 1H), 6.96 (d, 2H), 7.38-7.49  
9 (m, 2H), 7.81 (d, 1H), 7.99 (d, 1H), 8.04 (d, 2H), 8.26 (d, 1H)

10

## 11 EXAMPLE 58

12 Preparation of 1-[{2-(morpholin-4-yl)ethoxy}phenyl-4-sulfonyl]-5-methoxy-2-  
13 [[{(3,5-dimethyl-4-methoxy-2-pyridyl)methyl}sulfinyl]-1H-benzimidazole and 1-  
14 [{2-(morpholin-4-yl)ethoxy}phenyl-4-sulfonyl]-6-methoxy-2-[[{(3,5-dimethyl-4-  
15 methoxy-2-pyridyl)methyl}sulfinyl]-1H-benzimidazole

16 137 mg of [2-(Morpholin-4-yl)ethoxy]phenyl-4-sulfonyl chloride was added to  
17 172 mg of 5-methoxy-2-[[{(3,5-dimethyl-4-methoxy-2-pyridyl)methyl}sulfinyl]-  
18 1H-benzimidazole in dichloromethane (15 ml) and triethylamine (0.4 ml). The  
19 reaction mixture was stirred at room temperature overnight. The reaction mixture  
20 was washed with an aqueous solution composed of 0.1 M NaCl and 0.1 M sodium  
21 bicarbonate. Organic layer was dried over anhydrous magnesium sulfate, and  
22 evaporated. Residual material was lyophilized in vacuo to give 224 mg of the titled  
23 product (1:1 ratio).

24 NMR (CDCl<sub>3</sub>, δ): 2.22 (s, 3H), 2.30 (s, 3H), 2.50-2.51 (m, 4H), 2.79 (t, 2H), 3.69-  
25 3.74 (m, 4H; s, 3H), 3.82 & 3.91 (2s, total 3H), 4.12 (t, 2H), 4.78-4.94 (q, AB,  
26 2H), 6.93-7.08 (m, 3H), 7.46 (s, 1H), 7.68-7.86 (dd, 1H), 8.00-8.04 (m, 2H), 8.17  
27 (s, 1H)

28

## 1 EXAMPLE 59

2 Preparation of 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-2-[(3-  
3 methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole  
4 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl]sulfinyl]-1H-  
5 benzimidazole (185 mg) was dissolved in 20 ml of dichloromethane and 0.5 ml of  
6 triethylamine. 2-[2-(Morpholin-4-yl)ethoxy]ethoxyphenyl-4-sulfonyl chloride (163  
7 mg) was added and stirred at room temperature overnight. Dichloromethane layer  
8 was washed with an aqueous solution composed of 1 M NaCl and 0.1 N NaHCO<sub>3</sub>.  
9 Dichloromethane layer was dried over anhydrous magnesium sulfate. Solvent was  
10 removed under reduced pressure. Residual material was separated by preparative  
11 TLC. 198 mg of the titled product was obtained.

12 NMR (CDCl<sub>3</sub>, δ): 2.30 (s, 3H), 2.48 (m, 4H), 2.58 (t, 2H), 3.64-3.77 (m, 8H), 4.10  
13 (t, 2H), 4.34-4.40 (q, 2H), 4.81-5.01 (q, AB, 2H), 6.62 (d, 1H), 6.94 (d, 2H), 7.35-  
14 7.47 (m, 2H), 7.78 (d, 1H), 7.96 (d, 1H), 8.02 (d, 2H), 8.22 (d, 1H)

15

## 16 EXAMPLE 60

17 Preparation of 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]- 5-  
18 methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-  
19 benzimidazole and 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-  
20 6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-  
21 benzimidazole

22 162 mg of [2-{2-(morpholin-4-yl)ethoxy}ethoxy]benzene-4-sulfonyl chloride was  
23 added to 172 mg of 5-Methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-  
24 pyridyl)methyl]sulfinyl]-1H-benzimidazole in dichloromethane (15 ml) and  
25 triethylamine (0.5 ml). The reaction mixture was stirred at room temperature  
26 overnight. The reaction mixture was washed with an aqueous solution composed  
27 of 1 M NaCl and 0.1 M sodium bicarbonate. Organic layer was dried over  
28 anhydrous magnesium sulfate, and evaporated. Residual material was dried in

1 vacuo to give 254 mg of the titled product (1:1 ratio).

2 NMR (CDCl<sub>3</sub>, δ): 2.21 (s, 3H), 2.29 (s, 3H), 2.49-2.53 (m, 2H), 2.69-2.78 (m, 4H),  
3 3.67-3.89 (m, 8H; s, 3H; s, 3H), 4.07-4.13 (m, 2H), 4.76-4.93 (q, AB, 2H), 6.92-  
4 7.00 (m, 2H), 7.23 (d, 1H), 7.44 (d, 1H), 7.65-7.85 (dd, 1H), 7.98-8.03 (m, 2H),  
5 8.15 (s, 1H)

6

#### 7 EXAMPLE 61

8 Preparation of 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-2-  
9 [[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole  
10 2-[(3-Methyl-4-methoxypropoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole  
11 sodium salt (191mg) was dissolved in 20 ml of dichloromethane and 0.1 ml of  
12 triethylamine. 2-[2-(Morpholin-4-yl)ethoxy]ethoxyphenyl-4-sulfonyl chloride  
13 (163 mg) was added and stirred at room temperature overnight. Dichloromethane  
14 layer was washed with an aqueous solution composed of 1 M NaCl and 0.1 N  
15 NaHCO<sub>3</sub>. Dichloromethane layer was dried over anhydrous magnesium sulfate.  
16 Solvent was removed under reduced pressure. Residual material was lyophilized to  
17 give 253 mg of the titled product.

18 NMR (CDCl<sub>3</sub>, δ): 1.99-2.03 (m, 2H), 2.21 (s, 3H), 2.46 (t, 2H), 2.55 (t, 2H), 2.67  
19 (t, 2H), 3.29 (s, 3H), 3.48-3.53 (m, 2H), 3.64-3.68 (m, 6H), 3.73-3.74 (m, 2H),  
20 4.02-4.07 (m, 4H), 4.74-4.97 (q, AB, 2H), 6.62 (d, 1H), 6.89-6.92 (d, 2H), 7.31-  
21 7.42 (m, 2H), 7.75 (d, 1H), 7.93 (d, 1H), 8.02 (d, 2H), 8.13 (d, 1H)

22

#### 23 EXAMPLE 62

24 Preparation of N-(carbamoylmethyl)-2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-  
25 methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-  
26 yl)sulfonyl]phenoxy}acetamide and N-(carbamoylmethyl)-2-{4-[(6-methoxy-2-  
27 {[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-  
28 yl)sulfonyl]phenoxy}acetamide

1 Method 1) 5-Methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-  
2 1H-benzimidazole (172 mg) was dissolved in 20 ml of dichloromethane. Sodium  
3 tert-butoxide (55 mg) and N-(carbamoylmethyl)-2-[4-  
4 (chlorosulfonyl)phenoxy]acetamide (160 mg) was added. The reaction mixture  
5 was stirred at 30 °C for 36 hr. The reaction mixture was filtered. The filtrate was  
6 concentrated and treated with ethyl ether to give precipitates. Solid was collected,  
7 and dried in vacuo. 253 mg of the titled product (1:1 ratio) was obtained.

8 Method 2) 5-Methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-  
9 1H-benzimidazole (172 mg) was dissolved in 20 ml of dichloromethane and 0.4 ml  
10 of triethylamine. N-(carbamoylmethyl)-2-[4-(chlorosulfonyl)phenoxy]acetamide  
11 (160 mg) was added. The reaction mixture was stirred at 30 °C for 36 hr. The  
12 reaction mixture was treated with additional 80 ml of dichloromethane, and  
13 washed with 7% NaCl solution and 0.1 N sodium bicarbonate solution.  
14 Dichloromethane layer was dried over anhydrous magnesium sulfate and  
15 evaporated under reduced pressure. The residual material was lyophilized to give  
16 213 mg of the titled product (1:1 ratio).

17 NMR (DMSO-d<sub>6</sub>, δ): 2.14 (s, 3H), 2.25 (s, 3H), 3.34 (br, -NH, -NH<sub>2</sub>), 3.66 (d,  
18 2H), 3.70 (s, 3H), 3.88 (s, 3H), 4.67 (s, 2H), 4.81-5.08 (q, AB, 2H), 7.05-7.22 (m,  
19 3H), 7.35 (s, 1H), 7.89 (dd, 1H), 8.14-8.18 (m, 2H), 8.32 (s, 1H)  
20

#### 21 EXAMPLE 63

22 Preparation of N-(carbamoylmethyl)-2-(4-{[2-({[3-methyl-4-(2,2,2-  
23 trifluoroethoxy)-2-pyridyl]methyl}sulfinyl)benzimidazol-1-  
24 yl]sulfonyl}phenoxy)acetamide

25 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-  
26 benzimidazole (185 mg) was dissolved in 20 ml of dichloromethane and 0.5 ml of  
27 triethylamine, and N-(carbamoylmethyl)-2-[4-(chlorosulfonyl)phenoxy]acetamide  
28 (158 mg) was added. The reaction mixture was stirred at room temperature for 24

1 hr. Dichloromethane (100 ml) was added to the reaction mixture. The reaction  
2 mixture was washed with saturated NaCl solution, and 0.1 N sodium bicarbonate  
3 solution. Dichloromethane layer was separated and dried over anhydrous  
4 magnesium sulfate. Dichloromethane was evaporated under reduced pressure to  
5 give syrupy material, which was lyophilized in vacuo. 237 mg of the titled product  
6 was obtained.

7 NMR (DMSO-d<sub>6</sub>, δ): 2.23 (s, 3H), 3.36 (br, -NH<sub>2</sub>, -NH), 3.66 (d, 2H), 4.67 (s,  
8 2H), 4.84-5.17 (m, 2H and q, AB, 2H), 6.99-8.35 (m, 10H, aromatic H)

9  
10 EXAMPLE 64

11 Preparation of N-(carbamoylmethyl)-2-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-  
12 2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)acetamide  
13 2-[[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl)methyl]sulfinyl]-1H-  
14 benzimidazole sodium salt (190 mg) was dissolved in 20 ml of dichloromethane  
15 and 0.5 ml of triethylamine, and N-(carbamoylmethyl)-2-[4-  
16 (chlorosulfonyl)phenoxy]acetamide (160 mg) was added. The reaction mixture  
17 was stirred at room temperature for 24 hr. Dichloromethane (100 ml) was added to  
18 the reaction mixture. The reaction mixture was washed with saturated NaCl  
19 solution, and 0.1 N sodium bicarbonate solution. Dichloromethane layer was  
20 separated and dried over anhydrous magnesium sulfate. Dichloromethane was  
21 evaporated under reduced pressure to give syrupy material, which was lyophilized  
22 in vacuo. 215 mg of the titled product was obtained.

23 NMR (DMSO-d<sub>6</sub>, δ): 1.94-1.97 (m, 2H), 2.19 (s, 3H), 3.22 (s, 3H), 3.46 (t, 2H),  
24 3.67 (d, 2H), 4.06 (t, 2H), 4.68 (s, 2H), 4.84-5.14 (q, AB, 2H), 6.85 (d, 1H), 7.21  
25 (d, 2H), 7.42-7.55 (m, 2H), 7.80 (d, 1H), 7.91 (d, 1H), 8.02(d, 1H), 8.18(d, 2H)

26  
27 EXAMPLE 65

28 Preparation of 1-[(benzotriazol-1-yl)methyl]-5-methoxy-2-[[[(3,5-dimethyl-4-

1 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-[(benzotriazol-1-  
2 yl)methyl]- 6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-  
3 1H-benzimidazole  
4 5-Methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-  
5 benzimidazole (172 mg) was dissolved in 20 ml of dichloromethane. Sodium tert-  
6 butoxide (55 mg) and 1-(chloromethyl)-1H-benzotriazole (85 mg) was added. The  
7 reaction mixture was stirred at 30 °C for 3 days. TLC analysis (developing solvent;  
8 chloroform-methanol 15:1) showed major one spot of 1-[(benzotriazol-1-  
9 yl)methyl]- 5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-  
10 1H-benzimidazole above 5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-  
11 pyridyl)methyl]sulfinyl]-1H-benzimidazole. The titled product was purified by  
12 preparative thin layer chromatography. 195 mg of product, a mixture of 1-  
13 [(benzotriazol-1-yl)methyl]- 5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-  
14 pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-[(benzotriazol-1-yl)methyl]- 6-  
15 methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-  
16 benzimidazole was obtained (3:2 ratio).  
17 NMR (CDCl<sub>3</sub>, δ): 2.21 (s, 3H), 2.24 (s, 3H), 3.70 (s, 3H), 3.79 & 3.86 (2s, total  
18 3H), 4.85-5.08 (q, AB, 2H), 6.65 (d, 2H, N-CH<sub>2</sub>-N), 6.89-8.12 (m, 8H)  
19

#### 20 EXAMPLE 66

21 Preparation of 1-[(benzotriazol-1-yl)methyl-2-[[[(4-(3-methoxypropoxy)-3-  
22 methyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole  
23 2-[[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl)methyl]sulfinyl]-1H-  
24 benzimidazole sodium salt (190 mg) was dissolved in 20 ml of dichloromethane.  
25 1-(Chloromethyl)-1H-benzotriazole (85 mg) was added. The reaction mixture was  
26 stirred at 30 °C for 3 days. TLC analysis showed one spot of product. The reaction  
27 mixture was filtered. The filtrate was concentrated under reduced pressure, and  
28 treated with ethyl ether-heptane for precipitation. Precipitated solids were collected



1 and dried to give pure 1-[(benzotriazol-1-yl)methyl-2-[[[(4-(3-methoxypropoxy)-  
2 3-methyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (212 mg).  
3 NMR (CDCl<sub>3</sub>, δ): 2.05-2.08 (m, 2H), 2.21 (s, 3H), 3.34 (s, 3H), 3.54 (t, 2H), 4.08  
4 (t, 2H), 4.86-5.16 (q, AB, 2H), 6.69-6.70 (d, 2H, N-CH<sub>2</sub>-N), 7.00-8.15 (m, 10H)

5  
6 EXAMPLE 67

7 Preparation of diethyl [5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
8 pyridyl)methylsulfinyl]benzimidazol-1-yl]phosphate

9 5-Methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-  
10 benzimidazole (172 mg) was dissolved in 50 ml of dichloromethane and 0.5 ml of  
11 triethylamine. Diethyl chlorophosphate (87 mg) was added. The reaction mixture  
12 was stirred at room temperature for 18 hr. The reaction mixture was washed with  
13 saturated NaCl solution, and 0.1 N sodium bicarbonate solution twice times.  
14 Dichloromethane layer was separated and dried over anhydrous magnesium  
15 sulfate. Dichloromethane was evaporated under reduced pressure to give syrupy  
16 material, 215 mg of product. Syrupy product was slowly decomposed.  
17 NMR (CDCl<sub>3</sub>, δ): 1.28-1.38 (m, 6H), 2.10 (s, 3H), 2.19(s, 3H), 3.60 (s, 3H), 3.83  
18 (s, 3H), 4.20-4.28 (m, 4H), 4.72-4.87 (q, AB, 2H), 6.91 (d, 1H), 7.7 (d, 1H), 7.92  
19 (s, 1H), 8.18 (s, 1H)

20

21 CHEMICAL STABILITY

22 The chemical stability of the compounds of the invention has been followed  
23 kinetically at low concentration at 37 °C in a buffer solution composed of 0.2 M  
24 NaCl, 50 mM sodium phosphate, pH 7.4, 2% bovine albumin serum, 5-10%  
25 methanol. The compounds of Example 1 and Example 19 were measured to have  
26 a half-life ( $t_{1/2}$ ) 3 hr  $\pm$  0.5 hr and 3.5 hr  $\pm$  0.3 hr, respectively. The compound of  
27 Example 1 has slightly higher solubility in aqueous buffer than the compound of  
28 Example 19. The solubility of these compounds was found to affect their rate of

1 hydrolysis.

2 Acid stability of the compounds was assayed in 95% methanol containing 0.1 N  
3 HCl. Approximately 90% of the compound of Example 1 was still present intact  
4 (without decomposition) after 2.25 hour in this solution.

#### 5 BIOLOGICAL ASSAY

6 Inhibition of ATPase activity was measured using isolated hog gastric vesicles.  
7 The gastric H,K-ATPase (10  $\mu$ g) was incubated at 37 °C in a solution (1 ml)  
8 composed of 0.25 M sucrose, 20 mM Pipes/Tris, pH 7.4, 0.15 M KCl, 2 mM  
9  $MgCl_2$ , valinomycin 2  $\mu$ g/ml, and various concentration of compounds of the  
10 invention. At timed intervals, ATP was added (up to 2 mM) and incubated for 15  
11 minutes and amount of released phosphate ion was measured. As a control  
12 experiment the prior art drug without a labile group on the benzimidazole nitrogen  
13 (*e. g.* OMEPRAZOLE or LANSOPRAZOLE) was used for measuring inhibition  
14 of enzyme activity. Initially (before it underwent hydrolysis), the samples having  
15 10, 20, 50, and 100  $\mu$ M of the compound of Example 1 failed to inhibit enzyme  
16 activity. After 80 minutes however, the sample having 10  $\mu$ M of the compound of  
17 Example 1 inhibited 10% and the sample having 50  $\mu$ M inhibited 50%. In samples  
18 having 10  $\mu$ M of OMEPRAZOLE (control) and 10  $\mu$ M of the compound of  
19 Example 1, the same level of inhibition was obtained after 5.75 hours of  
20 hydrolysis.

#### 21 RELATIVE PLASMA CONCENTRATION OF OMEPRAZOLE IN MALE RAT

22 Male adult rats of the Sprague-Dawley strain were used for determining the  
23 concentration of OMEPRAZOLE in the plasma. All rats were deprived of food but  
24 not of water for one day. Example compounds (2 mg/kg of rat weight) were orally  
25 administered to male rats (weighing 250 g to 270 g) and blood samples (0.3 ml)  
26 were taken at timed intervals. Blood samples were centrifuged and plasma was  
27 taken out. Plasma was extracted with 0.5 ml of dichloromethane. Dichloromethane  
28 layer was evaporated by nitrogen/air blowing. The residual materials were

1 dissolved in 0.5 ml of 40% acetonitrile in 10 mM phosphate buffer (pH 7.4).  
2 Amounts of OMEPRAZOLE were determined by HPLC analysis. As a control,  
3 OMEPRAZOLE (4 mg/kg of rat weight) was orally administrated.

4

5 TABLE 3 : Relative concentration of OMEPRAZOLE released in the plasma  
6 (arbitrary unit)

7 min	EXAMPLE 29	EXAMPLE 33	EXAMPLE 37	omeprazole
8 20	4.5	2.5	1.67	28
9 40	14	34	14.36	4
10 60	8.5	13	3.5	2
11 80	3.5	4	1.88	1
12 100	2.5	2	1.88	N/D*
13 120	1.875	2	1.5	N/D*
14 140	0.625	1.5	1.5	
15 160	0.6	1	1	
16 180	0.6	1	1	
17 210	1.5	1	0.7	
18 240	0.5	1	0.7	
19 270	0.5	0.5	0.7	
20 300	0.2	0.5	0.4	
21 330	0.1	0.3	0.2	
22 360	0.05	0.3	0.1	
23 390	N/D	0.2	0.1	
24 430		0.1	N/D	

25 \* N/D : non-detectable.

26

27

28 TIME COURSES OF INHIBITORY EFFECT ON GASTRIC ACID SECRETION  
29 OF THE CONSCIOUS MALE RAT

30

31 Male rats (the Sprague-Dawley strain) are used. OMEPRAZOLE (2 mg) or  
32 Example 33 compound (1 mg) was resuspended in 1 ml of 15% sugar and 20 mM  
33 sodium phosphate buffer, pH 7.4. OMEPRAZOLE (2 mg/kg) or compound of  
34 Example 33 (1 mg/kg) was orally administrated. At timed intervals (2, 3.5, and 5

1 hr), the abdomen of the rat was incised and the pylorus was ligated under light ether anesthesia. Histamine (2 mg/kg) was intravenously injected for acid stimulation. Immediately the abdomen was closed. One hour later, the stomach was removed after ligation of the esophagus. The gastric juice was collected and acid output was quantified by titration using 0.1 N NaOH solution. As a control experiment, 1 ml of 15% sugar and 20 mM phosphate buffer solution was orally administered without any compounds (inhibitors). Acid output was quantified by same method as described above, showing maximum histamine-stimulated gastric acid secretion. Percentage inhibition was calculated from the fractional responses elicited by test compound and a control experiment. Further calculations are based on group mean responses from 3-4 rats.

12

13 TABLE 4: Inhibition of gastric acid secretion at the timed intervals

14	Time course	OMEPRazole (2	Example 33 (1 mg/kg,
		mg/kg, p.o.)	p.o.)
15	2 hr	90 %	84 %
16	3.5 hr	46 %	71 %
17	5 hr	45 %	91 %

18

19 The compound of Example 33 showed long duration of inhibition compared to  
20 OMEPRazole. Maximum inhibition by the compound of Example 33 was  
21 obtained after 5 hours, which shows that the compound of the invention is  
22 continuously converted to the corresponding PPI in vivo and inhibits gastric acid  
23 secretion.

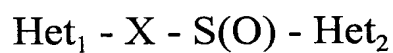
24

25

26

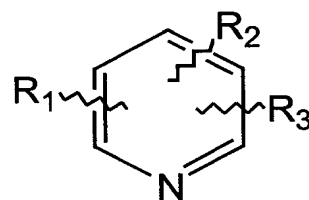
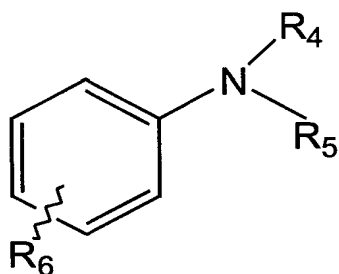
## WHAT IS CLAIMED IS:

1. A compound of the formula

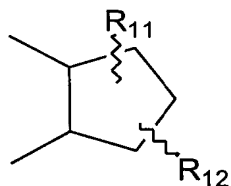
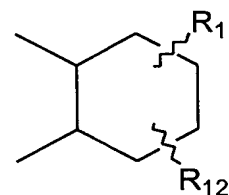
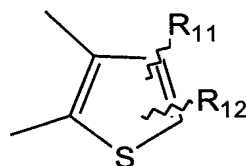
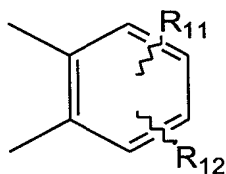
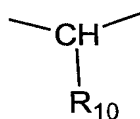


wherein

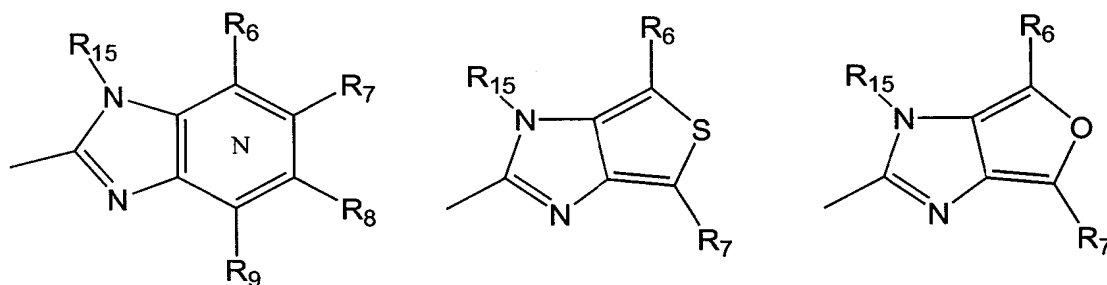
Het<sub>1</sub> is selected from the group consisting of the structures shown by the formulas below



X is selected from the group consisting of the structures shown by the formulas below



1 and Het<sub>2</sub> is selected from the group consisting of the structures shown by  
2 the formulas below



12 where N in the benzimidazole moiety represents that one of the ring carbons  
13 may be exchanged for an unsubstituted N atom;

14 R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are independently selected from hydrogen, alkyl of 1 to  
15 10 carbons, fluoro substituted alkyl of 1 to 10 carbons, alkoxy of 1 to 10 carbons,  
16 fluoro substituted alkoxy of 1 to 10 carbons, alkylthio of 1 to 10 carbons, fluoro  
17 substituted alkylthio of 1 to 10 carbons, alkoxyalkoxy of 2 to 10 carbons, amino,  
18 alkylamino and dialkylamino each of the alkyl groups in said alkylamino and  
19 dialkyl amino groups having 1 to 10 carbons, halogen, phenyl, alkyl substituted  
20 phenyl, alkoxy substituted phenyl, phenylalkoxy, each of the alkyl groups in said  
21 alkyl substituted phenyl, alkoxy substituted phenyl and phenylalkoxy having 1 to  
22 10 carbons, piperidino, morpholino or two of the R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> groups jointly  
23 forming a 5 or 6 membered ring having 0 or 1 heteroatom selected from N, S and  
24 O;

25 R<sub>4</sub> and R<sub>5</sub> are independently selected from hydrogen, alkyl of 1 to 10  
26 carbons, fluoro substituted alkyl of 1 to 10 carbons, phenylalkyl, naphthylalkyl and  
27 heteroarylalkyl, alkyl in said phenylalkyl, naphthylalkyl and heteroarylalkyl  
groups having 1 to 10 carbons;

1  $R_6$  is hydrogen, halogen, alkyl of 1 to 10 carbons, fluoro substituted alkyl  
 2 of 1 to 10 carbons, alkoxy having 1 to 10 carbons or fluoro substituted alkoxy  
 3 having 1 to 10 carbons;

4  $R_6$  through  $R_9$  are independently selected from hydrogen, alkyl of 1 to 10  
 5 carbons, halogen substituted alkyl of 1 to 10 carbons, alkoxy of 1 to 10 carbons,  
 6 halogen substituted alkoxy of 1 to 10 carbons, alkylcarbonyl, alkoxycarbonyl the  
 7 alkyl group in said alkylcarbonyl and alkoxycarbonyl having 1 to 10 carbons,  
 8 oxazolyl, imidazolyl, thiazolyl, pyrazolyl, or any two adjacent ones of the  $R_6$   
 9 through  $R_9$  groups may form a ring that may optionally include a heteroatom  
 10 selected from N, O and S and said ring may be further substituted;

11  $R_{10}$  is hydrogen, alkyl of 1 to 10 carbons, or  $R_{10}$  may form an alkylene  
 12 chain together with  $R_3$ ,

13  $R_{11}$  and  $R_{12}$  are independently selected from hydrogen, halogen, alkyl of  
 14 1 to 10 carbons and halogen substituted alkyl of 1 to 10 carbons;

15  $R_{15}$  is selected from the group consisting of the structures shown by the  
 16 formulas below

17

18

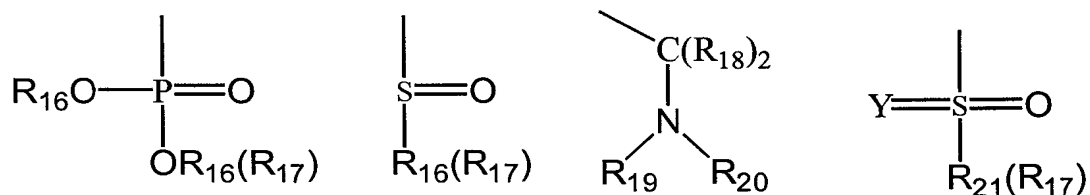
19

20

21

22

23



23 where

24  $R_{16}$  is alkyl of 1 to 10 carbons, morpholino, piperidino, phenyl, naphthyl  
 25 or heteroaryl having 1 to 3 heteroatoms selected from N, O or S, said morpholino.  
 26 piperidino phenyl, naphthyl or heteroaryl groups being unsubstituted, or  
 27 substituted with 1 to 5  $R_{17}$  groups;

1  $R_{17}$  is alkyl of 1 to 10 carbons, halogen substituted alkyl of 1 to 10  
 2 carbons, alkoxy having 1 to 10 carbons, halogen substituted alkoxy of 1 to 10  
 3 carbons, alkylthio having 1 to 10 carbons, halogen substituted alkylthio of 1 to 10  
 4 carbons, alkoxy carbonyl having 1 to 10 carbons, halogen substituted alkoxy  
 5 carbonyl having 1 to 10 carbons, F, Cl, Br, I,  $NO_2$ , CN, OCOalkyl,  $NH_2$ ,  
 6 alkylamino and dialkylamino where in said OCOalkyl, , alkylamino and  
 7 dialkylamino groups each of said alkyl group has 1 to 10 carbons, ureidoyl  
 8 (RNHCONH-), guanidiny, carbamoyl, N-substituted carbamoyl, alkylcarbamoyl  
 9 having 1 to 10 carbons, (alkoxycarbonyl)alkoxy groups of each of said alkoxy  
 10 group has 1 to 10 carbons, (alkoxycarbonyl)alkyl groups of each of said alkoxy or  
 11 alkyl group has 1 to 10 carbons, (carbamoyl)alkoxy having 1 to 10 carbons, (N-  
 12 alkylcarbamoyl)alkoxy having 1 to 10 carbons, (N,N-dialkylcarbamoyl)alkoxy  
 13 having 1 to 10 carbons, (N-substituted or unsubstituted carbamoyl)poly(alkoxy)  
 14 having 1 to 10 carbons, (N-substituted or unsubstituted carbamoyl)alkyl having 1  
 15 to 10 carbons, [N-(heteroaryl)carbamoyl]alkyl having 1 to 10 carbons, [N-  
 16 (heteroaryl)carbamoyl]alkoxy having 1 to 10 carbons, [N-(substituted  
 17 heteroaryl)carbamoyl]alkoxy having 1 to 10 carbons, [N-(substituted  
 18 aryl)carbamoyl]alkoxy having 1 to 10 carbons, poly(alkoxy) group of each of said  
 19 alkoxy group has 1 to 10 carbons, cyclic polyalkoxy (such as crown ether moiety),  
 20 guanidiny group, ureido group, dialkylamino-poly(alkoxy) group, [N-  
 21 (carbamoylalkyl)carbamoyl]alkoxy, [N-(carbamoylalkyl)carbamoyl]alkyl, [N-[[N-  
 22 (heteroaryl) carbamoyl]alkyl]carbamoyl]alkoxy, [N-[[N-(substituted heteroaryl)  
 23 carbamoyl]alkyl]carbamoyl]alkoxy, (sulfonato)alkyl, (sulfonato)alkoxy, N-  
 24 [sulfonato)alkyl]amido, (substituted)maleimido-, (substituted)succinimido [(tri-  
 25 alkyl)ammonium]-alkoxy;  
 26  $R_{18}$  is independently selected from H, alkyl of 1 to 10 carbons and phenyl;  
 27  $R_{19}$  and  $R_{20}$  are independently selected from H, alkyl of 1 to 10 carbons,  
 28 halogen substituted alkyl of 1 to 10 carbons, or  $R_{19}$  and  $R_{20}$  together with the N



1 atom may form a 4 to 10 membered ring that may include one more heteroatom  
 2 selected from N, O or S, said N heteroatom being unsubstituted or substituted with  
 3 an alkyl group of 1 to 10 carbons, or with an aryl or heteroaryl group, and

4  $R_{21}$  is alkyl, (aryl)alkyl, (heteroaryl)alkyl, phenyl, naphthyl or heteroaryl  
 5 where heteroaryl has 1 to 3 heteroatoms independently selected from N, O and S,  
 6 said phenyl, naphthyl or heteroaryl groups being unsubstituted or substituted with  
 7 1 to 5  $R_{17}$  groups,

8 Y is O or  $=NR_{16}$ ,

9 or to a pharmaceutically acceptable salt of said compound.

10 2. A compound in accordance with Claim 1 where **Het<sub>1</sub>** represents a  
 11 substituted pyridyl group.

12 3. A compound in accordance with Claim 1 where **Het<sub>2</sub>** represents a a  
 13 substituted benzimidazole group.

14 4. A compound in accordance with Claim 1 where X represents a  $CH_2$   
 15 group.

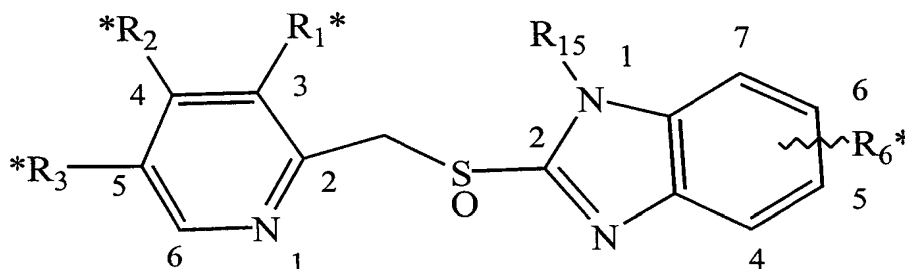
16 5. A compound in accordance with Claim 1 where  $R_{15}$  is  $R_{16}(R_{17})SO-$ .

17 6. A compound in accordance with Claim 1 where  $R_{15}$  is  
 18  $-C(R_{18})_2-N(R_{19}R_{20})$ .

19 7. A compound in accordance with Claim 1 where  $R_{15}$  is  $SO_2(R_{21})(R_{17})$ .

20 8. A compound in accordance with Claim 7 where  $R_{21}$  is phenyl,  
 21 pyridyl, thiophenyl, thiazolyl, or imidazolyl.

22 9. A compound of the formula



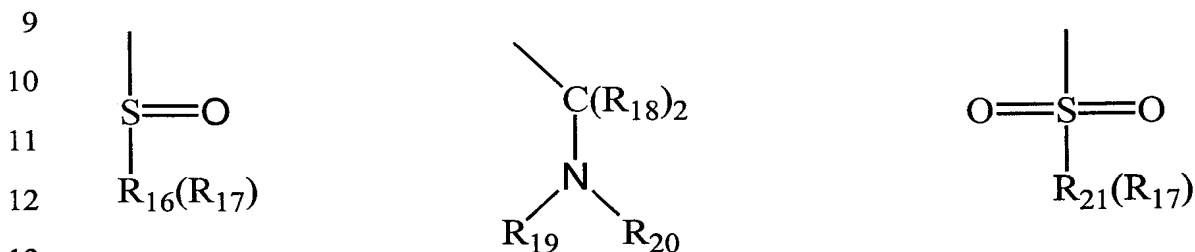
1 wherein  $R_6^*$  is H, methoxy or difluoromethoxy group in the 5 or in the 6  
2 position of the benzimidazole moiety;

3  $R_1^*$  is methyl, methoxy or chloro;

4  $R_2^*$  is methoxy, 2,2,2-trifluoroethoxy, 4-morpholino, ethylthio or  
5 (2,2,3,3,4,4,4-heptafluorobutyl)oxy;

6  $R_3^*$  is H or methyl, and

7  $R_{15}$  is selected from the group consisting of the structures shown by the  
8 formulas below



15 where

16  $R_{16}$  is alkyl of 1 to 10 carbons, morpholino, piperidino, phenyl, naphthyl  
17 or heteroaryl having 1 to 3 heteroatoms selected from N, O or S, said morpholino.  
18 piperidino phenyl, naphthyl or heteroaryl groups being unsubstituted, or  
19 substituted with 1 to 5  $R_{17}$  groups;

20  $R_{17}$  is alkyl of 1 to 10 carbons, halogen substituted alkyl of 1 to 10  
21 carbons, alkoxy having 1 to 10 carbons, halogen substituted alkoxy of 1 to 10  
22 carbons, alkylthio having 1 to 10 carbons, halogen substituted alkylthio of 1 to 10  
23 carbons, alkoxy carbonyl having 1 to 10 carbons, halogen substituted alkoxy  
24 carbonyl having 1 to 10 carbons, F, Cl, Br, I,  $\text{NO}_2$ , CN, OCOalkyl,  $\text{NH}_2$ ,  
25 alkylamino and dialkylamino where in said OCOalkyl, , alkylamino and  
26 dialkylamino groups each of said alkyl group has 1 to 10 carbons, further  $R_{17}$  is  
27 ureidoyl ( $\text{RNHCONH-}$ ), guanidinyl, carbamoyl, N-substituted carbamoyl,  
28 alkylcarbonyl having 1 to 10 carbons, (alkoxycarbonyl)alkoxy groups of each of

1 said alkoxy group has 1 to 10 carbons, (alkoxycarbonyl)alkyl groups of each of  
2 said alkoxy or alkyl group has 1 to 10 carbons, (carbamoyl)alkoxy having 1 to 10  
3 carbons, (N-alkylcarbamoyl)alkoxy having 1 to 10 carbons, (N,N-  
4 dialkylcarbamoyl)alkoxy having 1 to 10 carbons, (N-substituted or unsubstituted  
5 carbamoyl)poly(alkoxy) having 1 to 10 carbons, (N-substituted or unsubstituted  
6 carbamoyl)alkyl having 1 to 10 carbons, [N-(heteroaryl)carbamoyl]alkyl having 1  
7 to 10 carbons, [N-(heteroaryl)carbamoyl]alkoxy having 1 to 10 carbons, [N-  
8 (substituted heteroaryl)carbamoyl]alkoxy having 1 to 10 carbons, [N-(substituted  
9 aryl)carbamoyl]alkoxy having 1 to 10 carbons, poly(alkoxy) group of each of said  
10 alkoxy group has 1 to 10 carbons, cyclic polyalkoxy (such as crown ether moiety),  
11 guanidinyll group, ureido group, dialkylamino-poly(alkoxy) group, [N-  
12 (carbamoylealkyl)carbamoyl]alkoxy, [N-(carbamoylealkyl)carbamoyl]alkyl, [N-[[N-  
13 (heteroaryl) carbamoylealkyl]carbamoyl]alkoxy, [N-[[N-(substituted heteroaryl)  
14 carbamoylealkyl]carbamoyl]alkoxy, [(tri-alkyl)ammonium]-alkoxy,  
15 (sulfonato)alkyl, (sulfonato)alkoxy, N-[sulfonato)alkyl]amido,  
16 (substituted)maleimido-, (substituted)succinimido;

17  $R_{18}$  is independently selected from H, alkyl of 1 to 10 carbons and phenyl;

18  $R_{19}$  and  $R_{20}$  are independently selected from H, alkyl of 1 to 10 carbons,  
19 halogen substituted alkyl of 1 to 10 carbons, or  $R_{19}$  and  $R_{20}$  together with the N  
20 atom may form a 4 to 10 membered ring that may include one more heteroatom  
21 selected from N, O or S, said N heteroatom being unsubstituted or substituted with  
22 an alkyl group of 1 to 10 carbons, or with an aryl or heteroaryl group, and

23  $R_{21}$  is alkyl, (aryl)alkyl, (heteroaryl)alkyl, phenyl, naphthyl or heteroaryl  
24 having 1 to 3 heteroatoms independently selected from N, O and S, said phenyl,  
25 naphthyl or heteroaryl groups being unsubstituted or substituted with 1 to 5  $R_{17}$   
26 groups,

27 or to a pharmaceutically acceptable salt of said compound.

28 **10.** A compound in accordance with Claim 9 where  $R_{15}$  is  $R_{16}(R_{17})SO-$ .

1           **11.**   A compound in accordance with Claim 10 where  $R_{16}(R_{17})$  phenyl,  
2 substituted or unsubstituted with the  $R_{17}$  group.

3           **12.**   A compound in accordance with Claim 11 where  $R_{17}$  is selected  
4 from Cl, Br, F, lower alkyl, lower alkoxy, trifluoromethyl, trifluoromethoxy, di-  
5 (lower alkyl)amino, and lower alkoxycarbonyl.

6           **13.**   A compound in accordance with Claim 11 where  $R_{16}$  is unsubstituted  
7 or where  $R_{17}$  is selected from Cl, Br, F, methyl, methoxy, trifluoromethyl,  
8 trifluoromethoxy, dimethylamino and ethoxycarbonyl.

9           **14.**   A compound in accordance with Claim 9 where  $R_{15}$  is  
10  $R_{19}R_{20}N-C(R_{18})_2$ .

11           **15.**   A compound in accordance with Claim 14 where  $R_{18}$  is H or lower  
12 alkyl, and  $R_{19}R_{20}N$  represents di-(lower alkyl)amino, *N*-succinimidyl, *N*-  
13 morpholinyl, *N*-piperidinyl, *N*-(*N*-4-methyl)hexahydropyrazinyl, *N*,*N*-  
14 phenyl,methyl-amino, *N*-tetrahydropyrrolyl or *N*-(benzotriazol-1-yl).

15           **16.**   A compound in accordance with Claim 15 where  $R_{19}R_{20}N$  represents  
16 dimethylamino, *N*-morpholino, and *N*-piperidinyl.

17           **17.**   A compound in accordance with Claim 9 where  $R_{15}$  is  $R_{21}(R_{17})SO_2$ .

18           **18.**   A compound in accordance with Claim 17 where  $R_{21}(R_{17})$  is phenyl,  
19 thienyl or pyridyl, substituted or unsubstituted with the  $R_{17}$  group.

20           **19.**   A compound in accordance with Claim 18 where  $R_{17}$  is selected  
21 from Cl, Br, F, lower alkyl, lower alkoxy, trifluoromethyl, trifluoromethoxy, di-  
22 (lower alkyl)amino, lower alkoxycarbonyl, carbamoyl, guanidinyl, ureidoyl,  
23 (carbamoyl)alkoxy, [N-(heteroaryl)carbamoyl]alkoxy, morpholinyl, (morpholin-  
24 4-yl)alkoxy, [(morpholin-4-yl)alkoxy]alkoxy, (di-(lower alkyl)amino)alkoxy, [N-  
25 [(carbamoyl) alkyl]carbamoyl]alkoxy, poly(alkoxy), sodium(sulfonato)alkoxy,  
26 (trimethylammonium)alkoxy, and cyclic tetra- or penta-ethyleneoxy.

27           **20.**   A compound in accordance with Claim 18  $R_{21}$  is unsubstituted or  
28 where  $R_{17}$  is selected from Cl, Br, F, lower alkyl, lower alkoxy, trifluoromethyl,

1 di-(lower alkyl)amino, lower alkoxycarbonyl, carbamoyl, guanidiny, ureido,yl,  
2 (carbamoyl)methoxy, [N-(pyridyl)carbamoyl]methoxy, morpholinyl, (morpholin-  
3 4-yl)alkoxy, [(morpholin-4-yl)alkoxy]alkoxy, 2-(dimethylamino)ethoxy, [N-  
4 [(carbamoyl) methyl]carbamoyl]methoxy, poly(alkoxy), and cyclic tetra- or penta-  
5 ethyleneoxy group.

6 **21.** A compound in accordance with Claim 9, selected from the group  
7 consisting of:

8 1-benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
9 pyridyl)methylsulfinyl]-1H-benzimidazole,  
10 1-benzenesulfonyl-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
11 pyridyl)methylsulfinyl]-1H-benzimidazole,  
12 1-benzenesulfonyl-5-difluoromethoxy-2-[(3,4-dimethoxy-2-  
13 pyridyl)methylsulfinyl]-1H-benzimidazole,  
14 1-benzenesulfonyl-6-difluoromethoxy-2-[(3,4-dimethoxy-2-  
15 pyridyl)methylsulfinyl]-1H-benzimidazole,  
16 1-benzenesulfonyl-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-  
17 pyridyl)methylsulfinyl]-1H-benzimidazole,  
18 1-(p-chlorobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
19 pyridyl)methylsulfinyl]-1H-benzimidazole,  
20 1-(p-chlorobenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-  
21 pyridyl)methylsulfinyl]-1H-benzimidazole,  
22 1-(p-chlorobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-  
23 pyridyl)methylsulfinyl]-1H-benzimidazole,  
24 1-(p-chlorobenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-  
25 pyridyl)methylsulfinyl]-1H-benzimidazole,  
26 1-(p-chlorobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-  
27 pyridyl)methylsulfinyl]-1H-benzimidazole,  
28 1-(p-bromobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-

- 1 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 2 1-(p-bromobenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 3 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 4 1-(p-bromobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 5 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 6 1-(p-bromobenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 7 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 8 1-(p-bromobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 9 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 10 1-(p-fluorobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 11 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 12 1-(p-fluorobenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 13 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 14 1-(p-fluorobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 15 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 16 1-(p-fluorobenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 17 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 18 1-(p-fluorobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 19 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 20 1-(p-methylbenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 21 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 22 1-(p-methylbenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 23 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 24 1-(p-methylbenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 25 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 26 1-(p-methylbenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 27 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 28 1-(p-methylbenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-

- 1 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 2 1-(p-methoxybenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 3 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 4 1-(p-methoxybenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 5 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 6 1-(p-methoxybenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 7 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 8 1-(p-methoxybenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 9 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 10 1-(p-methoxybenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 11 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 12 1-(3-trifluoromethylbenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 13 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 14 1-(3-trifluoromethylbenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 15 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 16 1-(3-trifluoromethylbenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 17 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 18 1-(3-trifluoromethylbenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 19 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 20 1-(3-trifluoromethylbenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 21 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 22 1-(p-trifluoromethoxybenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 23 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 24 1-(p-trifluoromethoxybenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 25 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 26 1-(p-trifluoromethoxybenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 27 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 28 1-(p-trifluoromethoxybenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-

- 1 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 2 1-(p-trifluoromethoxybenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 3 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 4 1-(p-dimethylaminobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 5 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 6 1-(p-dimethylaminobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 7 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 8 1-(p-dimethylaminobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 9 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 10 1-(p-ethoxycarbonylbenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 11 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 12 1-(p-ethoxycarbonylbenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 13 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 14 1-(pyridine-3-sulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 15 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 16 1-(pyridine-3-sulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 17 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 18 1-(pyridine-3-sulfonyl)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
- 19 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 20 1-(pyridine-3-sulfonyl)-5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-
- 21 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 22 1-(pyridine-3-sulfonyl)-6-(difluoromethoxy)-2-[(3,4-dimethoxy-2-
- 23 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 24 1-[4-[(morpholin-4-yl)phenyl]sulfonyl]-5-methoxy-2-[(3,5-dimethyl-4-methoxy-
- 25 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 26 1-[4-[(morpholin-4-yl)phenyl]sulfonyl]-6-methoxy-2-[(3,5-dimethyl-4-methoxy-
- 27 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 28 N-[4-[[5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-



- 1 pyridyl)methyl]sulfinyl]benzimidazol-1-yl]sulfonyl]phenyl]urea,
- 2 N-[4-[[6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 3 pyridyl)methyl]sulfinyl]benzimidazol-1-yl]sulfonyl]phenyl]urea,
- 4 N-(4-{[2-([3-methyl-4-(2,2,2-trifluoroethoxy)-2-
- 5 pyridyl)methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenyl)urea,
- 6 N-(4-{[2-([4-(3-methoxypropoxy)-3-methyl-2-
- 7 pyridyl)methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenyl)urea,
- 8 N-(4-{[2-[[[(3,4-di(methoxy)-2-pyridyl)methyl]sulfinyl]-5-(difluoromethoxy)-
- 9 benzimidazol-1-yl]sulfonyl}phenyl)urea,
- 10 N-(4-{[2-[[[(3,4-di(methoxy)-2-pyridyl)methyl]sulfinyl]-6-(difluoromethoxy)-
- 11 benzimidazol-1-yl]sulfonyl}phenyl)urea,
- 12 15-{[2-([4-(3-methoxypropoxy-3-methyl-2-
- 13 pyridyl)methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}-
- 14 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
- 15 15-{[2-([3-methyl-4-(2,2,2-trifluoroethoxy)-2-
- 16 pyridyl)methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}-
- 17 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
- 18 15-[(5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-
- 19 pyridyl)methyl]sulfinyl}benzimidazol-1-yl]sulfonyl]-
- 20 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
- 21 15-[(6-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-
- 22 pyridyl)methyl]sulfinyl}benzimidazol-1-yl]sulfonyl]-
- 23 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
- 24 15-[(5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-
- 25 pyridyl)methyl]sulfinyl}benzimidazol-1-yl]sulfonyl]-
- 26 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
- 27 15-[(6-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-
- 28 pyridyl)methyl]sulfinyl}benzimidazol-1-yl]sulfonyl]-

- 1 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
- 2 2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
- 3 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
- 4 2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
- 5 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
- 6 pyridyl)acetamide,
- 7 N-(carbamoylmethyl)-2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
- 8 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
- 9 2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
- 10 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
- 11 2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
- 12 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
- 13 pyridyl)acetamide,
- 14 N-(carbamoylmethyl)-2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
- 15 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
- 16 2-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
- 17 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl} phenoxy)acetamide,
- 18 2-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
- 19 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl} phenoxy)-N-(2-
- 20 pyridyl)acetamide,
- 21 N-(carbamoylmethyl)-2-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
- 22 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl} phenoxy)acetamide,
- 23 2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-
- 24 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
- 25 2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-
- 26 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
- 27 pyridyl)acetamide,
- 28 N-(carbamoylmethyl)-2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-

- 1 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,  
2 2-{4-[(6-(difluoromethoxy)-2-[(3,4-dimethoxy-2-  
3 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,  
4 2-{4-[(6-(difluoromethoxy)-2-[(3,4-dimethoxy-2-  
5 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-  
6 pyridyl)acetamide,  
7 N-(carbamoylmethyl)-2-{4-[(6-(difluoromethoxy)-2-[(3,4-dimethoxy-2-  
8 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,  
9 2-(4-{2-([4-(3-methoxypropoxy)-3-methyl-2-  
10 pyridyl]methyl} sulfinyl)benzimidazol-1-yl)sulfonyl} phenoxy)acetamide,  
11 2-(4-{2-([4-(3-methoxypropoxy)-3-methyl-2-  
12 pyridyl]methyl} sulfinyl)benzimidazol-1-yl)sulfonyl} phenoxy)-N-(2-  
13 pyridyl)acetamide,  
14 N-(carbamoylmethyl)-2-(4-{2-([4-(3-methoxypropoxy)-3-methyl-2-  
15 pyridyl]methyl} sulfinyl)benzimidazol-1-yl)sulfonyl} phenoxy)acetamide,  
16 1-[[ 4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-5-(difluoromethoxy)-2-  
17 [[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,  
18 1-[[ 4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-6-(difluoromethoxy)-2-  
19 [[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,  
20 1-[[ 4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-5-methoxy-2-[(3,5-  
21 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,  
22 1-[[ 4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-6-methoxy-2-[(3,5-  
23 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,  
24 1-[[ 4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-2-[(3-methyl-4-  
25 methoxypropoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,  
26 1-[[ 4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-2-[(3-methyl-4-(2,2,2-  
27 trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,  
28 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-2-[[[4-(3-methoxypropoxy)-3-

- 1 methyl-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 2 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-5-(difluoromethoxy)-2-[(3,4-
- 3 dimethoxy-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 4 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-5-methoxy-2-[(3,5-dimethyl-4-
- 5 methoxy-2-pyridyl)methyl)sulfinyl]]-1H-benzimidazole,
- 6 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-6-(difluoromethoxy)-2-[(3,4-
- 7 dimethoxy-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 8 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-6-methoxy-2-[(3,5-dimethyl-4-
- 9 methoxy-2-pyridyl)methyl)sulfinyl]]-1H-benzimidazole,
- 10 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-2-[[[3-methyl-4-(2,2,2-
- 11 trifluoroethoxy)-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 12 1-[(N,N-dimethylamino)methyl]benzene-4-sulfonyl]-5-methoxy-2-[(3,5-
- 13 dimethyl-4-methoxy-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 14 1-[2-acetamido-4-methyl-5-thiazolylsulfonyl]-5-methoxy-2-[(3,5-dimethyl-4-
- 15 methoxy-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 16 1-(thiophene-2-sulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 17 pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 18 1-[(N,N-dimethylamino)methyl]benzene-4-sulfonyl]-6-methoxy-2-[(3,5-
- 19 dimethyl-4-methoxy-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 20 1-[2-acetamido-4-methyl-5-thiazolylsulfonyl]-6-methoxy-2-[(3,5-dimethyl-4-
- 21 methoxy-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 22 1-(thiophene-2-sulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 23 pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 24 1-(thiophene-2-sulfonyl)-2-[[[4-(3-methoxypropoxy)-3-methyl-2-
- 25 pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 26 1-(thiophene-2-sulfonyl)-5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-
- 27 pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 28 1-(thiophene-2-sulfonyl)-6-(difluoromethoxy)-2-[(3,4-dimethoxy-2-

- 1 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 2 1-(thiophene-2-sulfonyl)- ]- 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
- 3 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 4 1-(phenylmethylsulfonyl)-5-methoxy-2-[[[3,5-dimethyl-4-methoxy-2-
- 5 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 6 1-(n-propanesulfonyl)-5-methoxy-2-[[[3,5-dimethyl-4-methoxy-2-
- 7 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 8 1-(n-butanesulfonyl)-5-methoxy-2-[[[3,5-dimethyl-4-methoxy-2-
- 9 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 10 1-(isopropylsulfonyl)-5-methoxy-2-[[[3,5-dimethyl-4-methoxy-2-
- 11 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 12 1-[(N,N-dimethylamino)benzene-4-sulfonyl]-5-methoxy-2-[[[3,5-dimethyl-4-
- 13 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 14 1-(phenylmethylsulfonyl)-6-methoxy-2-[[[3,5-dimethyl-4-methoxy-2-
- 15 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 16 1-(n-propanesulfonyl)-6-methoxy-2-[[[3,5-dimethyl-4-methoxy-2-
- 17 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 18 1-(n-butanesulfonyl)-6-methoxy-2-[[[3,5-dimethyl-4-methoxy-2-
- 19 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 20 1-(isopropylsulfonyl)-6-methoxy-2-[[[3,5-dimethyl-4-methoxy-2-
- 21 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 22 1-[(N,N-dimethylamino)benzene-4-sulfonyl]-6-methoxy-2-[[[3,5-dimethyl-4-
- 23 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 24 1-(pyridine-3-sulfonyl)-2-[[[3-methyl-4-methoxypropoxy-2-
- 25 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 26 1-[4-(morpholin-4-yl)phenylsulfonyl]-2-[[[4-(3-methoxypropoxy)-3-methyl-2-
- 27 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 28 1-benzenesulfonyl-2-[[[3-chloro-4-morpholino-2-pyridyl)methyl]sulfinyl]-5-

- 1 methoxy-(1H)-benzimidazole,
- 2 1-benzenesulfonyl-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-
- 3 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 4 1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]-1H-benzimidazole,
- 5 1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]imidazolo[5,4-c]pyridine,
- 6 1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]imidazolo[4,5-c]pyridine,
- 7 1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]-5-nitro-benzimidazole,
- 8 1-benzenesulfonyl-2-[{2-(dimethylamino)phenyl}methylsulfinyl]-1H-
- 9 benzimidazole,
- 10 1-benznesulfonyl-2-[[[4-(2,2,3,3,4,4,4-heptafluorobutyl)oxy]-2-
- 11 pyridyl)methyl]sulfinyl]-1H-thieno[3,4-d]imidazole,
- 12 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]- 2-[(3-
- 13 methoxyphenyl)methylsulfinyl]imidazolo{5,4-c}pyridine,
- 14 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]- 2-[{2-
- 15 (dimethylamino)phenyl}methylsulfinyl]-1H-benzimidazole,
- 16 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]- 5-methoxy-2-[[{(3,5-
- 17 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 18 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]- 6-methoxy-2-[[{(3,5-
- 19 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 20 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-2-[[[(4-(3-
- 21 methoxypropoxy)-3-methyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 22 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-5-(difluoromethoxy)-
- 23 2-[[{(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 24 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-6-(difluoromethoxy)-
- 25 2-[[{(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 26 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]- 2-[[[3-methyl-4-
- 27 (2,2,2-trifluoroethoxy)-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 28 1-(benzotriazol-1-yl)methyl-5-methoxy-2-[[{(3,5-dimethyl-4-methoxy-2-

1 pyridyl)methyl]sulfinyl]-1H-benzimidazole,  
2 1-(benzotriazol-1-yl)methyl-6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-  
3 pyridyl)methyl]sulfinyl]-1H-benzimidazole,  
4 1-(benzotriazol-1-yl)methyl-2-[[[4-(3-methoxypropoxy)-3-methyl-2-  
5 pyridyl]methyl]sulfinyl]-1H-benzimidazole,  
6 diethyl [5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-  
7 pyridyl)methyl]sulfinyl]benzimidazol-1-yl]phosphate,  
8 1-(4-acetaminobenzenesulfonyl)-5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-  
9 pyridyl)methyl]sulfinyl]-1H-benzimidazole,  
10 1-(4-acetaminobenzenesulfonyl)-6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-  
11 pyridyl)methyl]sulfinyl]-1H-benzimidazole,

12       **22.** A pharmaceutical composition comprising a pharmaceutically  
13 acceptable excipient and a prodrug of a proton pump inhibitor in accordance with  
14 Claim 1.

15       **23.** A pharmaceutical composition comprising a pharmaceutically  
16 acceptable excipient and a prodrug of a proton pump inhibitor in accordance with  
17 Claim 9.

18       **24.** A pharmaceutical composition comprising a pharmaceutically  
19 acceptable excipient and a prodrug of a proton pump inhibitor in accordance with  
20 Claim 21.

21       **25.** A pharmaceutical composition in accordance with Claim 22, 23 or  
22 24, said composition comprising a liquid adapted for injection to a mammal, said  
23 liquid having a pH not exceeding 8.5 pH units.

24       **26.** A compound in accordance with Claim 1 where Het<sub>1</sub> is m-  
25 methoxyphenyl.

26

# INTERNATIONAL SEARCH REPORT

Int'l Application No  
PCT/US 99/18048

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/12 C07D401/14 C07D409/14 C07D417/14 C07D235/28  
C07D471/04 A61K31/4184 A61K31/4439

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 045 200 A (UPJOHN CO) 3 February 1982 (1982-02-03) page 22, line 28; claims 1,7,9	1,22-25
X	GB 2 134 523 A (HAESSLE AB) 15 August 1984 (1984-08-15) page 18, line 3; claims 1,19; example 134; table 1	1,22-25
A	US 4 686 230 A (RAINER GEORG ET AL) 11 August 1987 (1987-08-11) cited in the application claims 1,21; examples	1,22-25

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

21 December 1999

Date of mailing of the international search report

11/01/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3018

Authorized officer

Bosma, P



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/18048

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0045200	A	03-02-1982	US 4359465 A	16-11-1982
			DE 3176664 A	07-04-1988
			JP 1060008 B	20-12-1989
			JP 1574094 C	20-08-1990
			JP 57053406 A	30-03-1982
GB 2134523	A	15-08-1984	AT 386825 B	25-10-1988
			AT 43584 A	15-03-1988
			AU 578891 B	10-11-1988
			AU 2445684 A	16-08-1984
			BE 898880 A	10-08-1984
			CH 666892 A	31-08-1988
			CY 1555 A	22-03-1991
			DE 3404610 A	16-08-1984
			DK 59184 A	12-08-1984
			FI 840547 A	12-08-1984
			FR 2543551 A	05-10-1984
			GB 2174988 A, B	19-11-1986
			IT 1177553 B	26-08-1987
			JP 59181277 A	15-10-1984
			LU 85209 A	12-09-1985
			NL 8400446 A	03-09-1984
			NO 840504 A	13-08-1984
			NO 882001 A	13-08-1984
			NZ 207102 A	30-09-1987
			SE 8400688 A	12-08-1984
			SE 8700498 A	10-02-1987
			SE 8700499 A	10-02-1987
			US 5039806 A	13-08-1991
			ZA 8401011 A	26-09-1984
US 4686230	A	11-08-1987	AT 79377 T	15-08-1992
			AU 5198886 A	15-05-1986
			DE 3586498 A	17-09-1992
			DK 308986 A	27-06-1986
			WO 8602646 A	09-05-1986
			EP 0201575 A	20-11-1986
			ES 548455 A	16-04-1987
			FI 862720 A	25-06-1986
			GR 852631 A	03-02-1986
			HU 40643 A	28-01-1987
			IL 76839 A	31-08-1988
			JP 7005588 B	25-01-1995
			JP 62500664 T	19-03-1987
			NO 862618 A	21-08-1986
			NZ 214005 A	27-10-1989
			PT 81396 A, B	01-11-1985